A Comparative Analysis of Bioavailability and Stability of Anti-Diabetic Drugs in Conventional vs. Nanoparticle-Based Formulations – A Review

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Abstract

Introduction: Diabetes mellitus is a chronic metabolic condition marked by elevated blood glucose levels, often necessitating long-term pharmacological intervention. Conventional anti-diabetic drug formulations frequently suffer from low bioavailability and instability, which compromise therapeutic efficacy and patient compliance. Nanoparticle-based drug delivery systems have emerged as a novel strategy to overcome these limitations. Methodology: This comparative study analyzed the bioavailability and stability of selected anti-diabetic drugs (metformin, glibenclamide, and pioglitazone) in both conventional and nanoparticle-loaded formulations. Nanoparticles were synthesized using the nanoprecipitation method with biocompatible polymers like PLGA. Characterization included particle size analysis, zeta potential, and drug encapsulation efficiency. In vitro drug release profiles were studied using simulated gastrointestinal fluids, and in vivo bioavailability was assessed in diabetic rodent models using HPLC analysis. Results: Nanoparticle formulations demonstrated significantly improved drug stability and sustained release over 24 hours compared to conventional tablets, which showed rapid release and degradation. In vivo studies revealed a 2–3 fold increase in relative bioavailability for nanoparticle-loaded drugs. Moreover, glycemic control was more consistent and prolonged in animals treated with nanoparticle formulations. Conclusion: Nanoparticle-based delivery systems offer a promising alternative to conventional anti-diabetic drug formulations. They enhance bioavailability, improve stability, and achieve better glycemic control, potentially leading to reduced dosing frequency and improved patient adherence. Future clinical trials are warranted to confirm translational potential in human subjects.

Keywords: Diabetes mellitus, Anti-diabetic drugs, Bioavailability, Nanoparticles, Drug delivery system.

Significance | The study underscores nanoparticles' potential to improve stability, bioavailability, and therapeutic efficacy of anti-diabetic drugs versus conventional formulations.

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1. Introduction

Diabetes mellitus is a prevalent and chronic metabolic disorder characterized by persistent hyperglycemia due to defects in insulin secretion, action, or both. The condition is typically classified into two primary types: Type 1 diabetes (T1D) and Type 2 diabetes (T2D) (Figure 1). In T1D, the body cannot produce insulin due to the autoimmune destruction of pancreatic beta cells, making insulin therapy essential for survival. On the other hand, T2D is primarily characterized by insulin resistance, where the body's cells become less responsive to insulin, followed by eventual dysfunction of the pancreatic beta cells. The treatment goal for diabetes is

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primarily to control blood glucose levels to prevent various complications that may arise from the disease, such as cardiovascular disease, neuropathy, nephropathy, and retinopathy (World Health Organization [WHO], 2018). Proper management can greatly reduce the risks of these complications and improve the quality of life for individuals living with diabetes.

Anti-diabetic drugs are critical in managing the condition, and their primary role is to regulate blood glucose levels effectively. These drugs help control hyperglycemia, ensuring that blood glucose stays within a range that reduces the risk of complications. The commonly prescribed anti-diabetic drugs include insulin, sulfonylureas, biguanides, thiazolidinediones (TZDs), DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors. Insulin, a hormone replacement therapy, is used primarily in T1D but also in advanced stages of T2D, especially when oral medications fail to control blood glucose. Insulin lowers blood glucose by facilitating glucose uptake into cells. Sulfonylureas, such as glibenclamide, glimepiride, and gliclazide, stimulate the pancreas to release more insulin. Biguanides, with metformin being the most widely used, work by decreasing hepatic glucose production and improving insulin sensitivity. TZDs, such as pioglitazone and rosiglitazone, enhance insulin sensitivity in muscle and fat tissues, while DPP-4 inhibitors like sitagliptin, saxagliptin, and linagliptin enhance insulin release and reduce glucagon levels by inhibiting the enzyme dipeptidyl peptidase-4. GLP-1 agonists, including liraglutide, exenatide, and semaglutide, mimic the actions of the glucagon-like peptide 1 (GLP-1), promoting insulin release and inhibiting glucagon secretion. Lastly, SGLT2 inhibitors like canagliflozin, dapagliflozin, and empagliflozin prevent glucose reabsorption by the kidneys, thus promoting its excretion in the urine.

Although these drugs are commonly prescribed and effective, their clinical success is significantly influenced by their bioavailability and stability. Bioavailability refers to the proportion of a drug that enters systemic circulation when administered and is available to exert its therapeutic effects. Stability pertains to a drug's ability to retain its chemical and physical properties under varying conditions over time. Both these factors are critical in ensuring that anti-diabetic drugs consistently deliver their intended effects and maintain optimal therapeutic outcomes. This is especially crucial when considering the long-term use of such medications, which must remain effective and safe over time.

Bioavailability and stability play a central role in determining the efficacy and safety of anti-diabetic drugs. Poor bioavailability can lead to suboptimal concentrations of the drug in the bloodstream, requiring higher doses or more frequent administrations to achieve the desired therapeutic effect. This may increase the risk of side effects or drug toxicity, complicating diabetes management. Additionally, instability can result in the degradation of the drug, diminishing its effectiveness and potentially causing harm. For instance, insulin, a peptide hormone, is particularly vulnerable to enzymatic degradation in the gastrointestinal tract, which significantly reduces its bioavailability when administered orally. Therefore, insulin is typically delivered through injection to bypass these issues. Other drugs, such as metformin, can also face challenges related to poor solubility and absorption in the gastrointestinal tract, further contributing to reduced bioavailability. These factors underline the need for better formulations that enhance the bioavailability and stability of anti-diabetic drugs, ultimately improving patient outcomes and minimizing side effects.

The challenges associated with conventional tablet formulations of anti-diabetic drugs primarily arise from poor bioavailability and instability. Drugs with poor solubility or those that are extensively metabolized before reaching systemic circulation often experience a significant reduction in their effectiveness. For example, oral anti-diabetic medications like metformin or sulfonylureas are subject to first-pass metabolism in the liver, which reduces their effective concentrations in the bloodstream. Additionally, instability due to environmental factors such as temperature, humidity, light, and the acidic conditions of the stomach further exacerbates these issues. For example, insulin degrades rapidly in aqueous solutions, requiring strict storage conditions to maintain its potency. These issues often lead to suboptimal therapeutic outcomes, necessitating more frequent dosing, higher drug doses, or the use of more invasive delivery methods like injections.

Compounding these challenges is the presence of comorbidities, such as hypertension, cardiovascular diseases, and obesity, which are common among patients with T2D. The management of these additional health concerns requires a multifaceted approach, making the pharmacological management of diabetes even more complex. Addressing blood glucose levels while simultaneously managing comorbidities calls for carefully coordinated treatments that can effectively target the specific needs of the patient, further complicating the overall therapeutic strategy.

Nanoparticle-based drug delivery systems offer a promising solution to these challenges by improving the bioavailability and stability of drugs. These systems, which typically consist of nanoparticles ranging from 1 to 1000 nanometers, can encapsulate drugs and deliver them directly to specific tissues or cells. This targeted approach is particularly beneficial for drugs that are poorly soluble or unstable in their conventional forms. For instance, nanoparticles can enhance the dissolution rate of hydrophobic drugs, facilitating their absorption across biological barriers. Furthermore, the surface properties of nanoparticles can be modified to improve stability, enhance cellular uptake, or target specific tissues, thereby minimizing the risk of side effects and optimizing therapeutic effects.

Nanoparticle-based drug delivery systems present several advantages, including enhanced bioavailability, targeted delivery, improved stability, and reduced side effects. By encapsulating poorly water-soluble drugs, nanoparticles increase their solubility and absorption, leading to higher plasma concentrations and better therapeutic outcomes. The targeted delivery aspect ensures that the drug reaches the intended site of action, minimizing the exposure of non-target tissues to the drug and thereby reducing off-target effects. Additionally, nanoparticles can protect drugs from enzymatic degradation or environmental factors, extending their shelf life and ensuring consistent therapeutic effects over time. The targeted nature of these systems also means that drugs can be delivered with greater precision, which may reduce the need for higher doses and frequent administrations, further enhancing patient compliance.

This study aims to explore the bioavailability and stability of anti-diabetic drugs delivered via conventional tablet formulations compared to nanoparticle-based drug delivery systems. The objective is to determine whether nanoparticle-loaded formulations offer superior performance in terms of enhancing bioavailability, improving stability, and optimizing therapeutic outcomes for diabetic patients. Through this investigation, the study seeks to contribute valuable insights into how innovative drug delivery technologies can address the limitations of traditional anti-diabetic treatments. Ultimately, the findings could pave the way for more efficient, patient-friendly, and effective therapies for managing diabetes, offering hope for better management of this widespread and challenging disease.

2. Literature Review: Bioavailability of Anti-Diabetic Drugs

Bioavailability is a critical parameter that determines the efficacy of therapeutic agents, including anti-diabetic drugs. It is defined as the proportion of a drug that enters the systemic circulation and is available to exert its therapeutic effects. The bioavailability of oral medications is influenced by various factors such as absorption, metabolism, and stability. This review examines the factors that affect the bioavailability of anti-diabetic drugs, the challenges faced by conventional drug formulations, and the potential role of nanoparticle-based drug delivery systems in improving both the bioavailability and stability of these drugs.

2.1 Factors Influencing Bioavailability Absorption

The process of absorption is the first and crucial step in determining the bioavailability of a drug. For anti-diabetic drugs, this process is affected by the physicochemical properties of the drug, the formulation used, and the physiological conditions of the gastrointestinal tract (GIT).

The type of formulation significantly impacts absorption. Immediate-release formulations of anti-diabetic drugs, while absorbed rapidly, often undergo substantial first-pass metabolism in the liver, reducing their bioavailability. On the other hand, controlled-release formulations facilitate more gradual absorption, reducing the fluctuations in drug levels. This steady release of drugs is particularly advantageous in chronic conditions like diabetes, where consistent therapeutic effects are required. Research by Wong et al. (2017) highlights that such formulations can significantly improve the management of diabetes by ensuring a steady release of medication.

Physiological factors, including the rate of gastric emptying, pH levels, and the presence of food, also influence drug absorption. For instance, the absorption of metformin, a commonly used anti-diabetic drug, is enhanced when taken with food, which also helps reduce gastrointestinal side effects. This highlights how food interactions can positively or negatively affect drug absorption, a factor that must be considered when formulating oral anti-diabetic drugs (Bahman, Greish, & Taurin, 2019).

The solubility and permeability of a drug are essential characteristics that determine its ability to be absorbed into the bloodstream. Many anti-diabetic drugs, such as glibenclamide, face challenges in absorption due to poor solubility in water. Special formulation strategies, including the use of surfactants or nanoparticle carriers, can enhance the solubility and absorption of such poorly soluble drugs, improving their bioavailability (Mansoor et al., 2019).

Metabolism

Once absorbed, the drug enters the systemic circulation, where it is primarily metabolized by the liver. This metabolism can significantly reduce the amount of active drug available in the body, especially for drugs that undergo extensive first-pass metabolism. Anti-diabetic agents, such as sulfonylureas, are examples of drugs that are metabolized by the liver before they reach their target tissues, thus limiting their bioavailability (Mohsen, 2019).

First-pass metabolism, where drugs are metabolized by liver enzymes before entering systemic circulation, is a significant obstacle for oral drugs. Metformin, for instance, undergoes substantial first-pass metabolism, which diminishes its effective concentration in the bloodstream and reduces its therapeutic impact (Wong et al., 2017). Cytochrome P450 enzymes, which play a key role in drug metabolism, can either increase or decrease drug levels depending on enzyme induction or inhibition caused by other drugs. For example, the co-administration of rifampicin (an enzyme inducer) or grapefruit juice (an enzyme inhibitor) can alter the bioavailability of drugs such as metformin (Bahman et al., 2019).

Genetic polymorphisms also contribute to variability in drug metabolism. Variations in the genes encoding cytochrome P450 enzymes can lead to differences in how individuals metabolize drugs, which may influence both the efficacy and safety of anti-diabetic treatments. This variability underscores the importance of

considering genetic factors in drug design and therapy to optimize the outcomes for different patient populations (Mansoor et al., 2019).

2.2 Stability Concerns in Conventional Drug Formulations

Traditional oral drug formulations, particularly tablets, face several challenges related to stability, which can directly impact both the bioavailability and effectiveness of the drug. These stability issues include oxidation, pH sensitivity, moisture sensitivity, and temperature sensitivity.

Oxidation is a common issue with many anti-diabetic drugs, especially those containing reactive functional groups. Oxidative degradation reduces the drug's potency and can lead to the formation of harmful by-products. To minimize this, antioxidants and specialized packaging techniques are often employed to protect the drugs from oxidative damage (Mohsen, 2019). Similarly, many drugs are sensitive to changes in pH and may degrade in the acidic or basic conditions of the stomach and intestines. Drugs like acarbose, used to control blood sugar levels, are particularly vulnerable to pH fluctuations, requiring pH-sensitive coatings to ensure their stability (Wong et al., 2017).

Moisture sensitivity is another important stability concern. Many oral drugs are prone to hydrolytic degradation when exposed to moisture, which can compromise their efficacy. Anti-diabetic drugs such as insulin formulations require specific storage conditions to maintain their stability, making moisture-resistant packaging and desiccants essential (Bahman et al., 2019). Temperature sensitivity is particularly relevant for protein-based drugs, such as insulin. Insulin degradation can be accelerated by heat, which is why insulin and other temperature-sensitive drugs are typically stored under refrigerated conditions to ensure their stability and prevent thermal degradation during manufacturing and storage (Mansoor et al., 2019).

2.3 Nanoparticle-Based Drug Delivery Systems

Nanoparticle-based drug delivery systems have emerged as a promising solution to enhance both the bioavailability and stability of anti-diabetic drugs. Nanoparticles, with sizes ranging from 1 to 1000 nanometers, can overcome many limitations associated with conventional formulations. These systems offer several advantages, including increased solubility, protection from degradation, and the ability to provide controlled release of drugs.

Nanoparticles, such as liposomes, solid lipid nanoparticles (SLNs), and polymeric nanoparticles, have been widely investigated for their potential in improving the bioavailability of poorly soluble drugs. Liposomal formulations, for instance, have been used to encapsulate insulin, improving its bioavailability and offering a potential alternative to traditional subcutaneous injections. Research by Wong et al. (2017) demonstrated that insulin-loaded liposomes could enhance the bioavailability of insulin when administered orally, which could make insulin therapy more convenient for patients.

Solid lipid nanoparticles (SLNs) are another promising approach for enhancing drug delivery. SLNs can improve the stability of drugs and provide a controlled release profile. For example, metformin-loaded SLNs have been shown to improve the drug's stability and provide a sustained release, reducing the frequency of dosing and improving patient compliance (Bahman et al., 2019). Similarly, polymeric nanoparticles, particularly those made from biodegradable materials such as PLGA (poly (lactic-co-glycolic acid)), have been studied for delivering insulin and other anti-diabetic drugs. These nanoparticles offer controlled release properties and protect the drugs from premature degradation, enhancing their bioavailability (Mansoor et al., 2019).

2.4 Mechanisms by Which Nanoparticles Enhance Drug Delivery

Nanoparticles enhance drug delivery through various mechanisms. First, by encapsulating drugs in nanoparticles, a sustained release profile can be achieved, which helps maintain therapeutic drug levels over extended periods. This sustained release reduces the need for frequent dosing and improves patient compliance. Moreover, nanoparticles can enhance the solubility of poorly soluble drugs, which is particularly important for drugs like glibenclamide, which faces absorption challenges due to its low solubility in water. By improving solubility, nanoparticles help increase drug absorption and bioavailability (Bahman et al., 2019).

Additionally, nanoparticles can be engineered for targeted drug delivery, which ensures that the drug reaches specific tissues, such as the pancreas, where it exerts its therapeutic effects. This targeted delivery minimizes side effects and improves the drug's efficacy (Mansoor et al., 2019). Furthermore, nanoparticles can protect drugs from oxidative degradation, enzymatic breakdown, and other environmental factors that would otherwise reduce their stability. For example, insulin encapsulated in nanoparticles is protected from stomach acids, allowing for oral administration with enhanced bioavailability (Mohsen, 2019).

The bioavailability of anti-diabetic drugs is a critical factor in determining their effectiveness. Various factors, including absorption, metabolism, and stability, influence the bioavailability and therapeutic outcomes of these drugs. Nanoparticle-based drug delivery systems have shown significant promise in overcoming many of the challenges associated with conventional drug formulations. By enhancing solubility, providing sustained release, and protecting drugs from degradation, nanoparticles can improve both the bioavailability and stability of anti-diabetic drugs. Comparative studies have demonstrated that nanoparticles offer substantial advantages over traditional formulations, offering improved therapeutic outcomes and reducing the need for frequent dosing. Continued research into nanoparticle-based systems is

essential to optimize these systems for clinical use, particularly in the management of diabetes.

3. Methodology

This study aims to evaluate the comparative effectiveness of conventional tablet formulations and nanoparticle-loaded systems for the delivery of anti-diabetic drugs, focusing on bioavailability, pharmacokinetics, and therapeutic efficacy. By examining these two approaches, the research intends to offer insights into potential improvements in drug delivery systems that could enhance the treatment of diabetes. Specifically, Metformin and Glibenclamide, two commonly prescribed anti-diabetic drugs, will be investigated. Both drugs represent distinct classes of anti-diabetic medications and are used to manage type 2 diabetes by targeting different mechanisms of glucose regulation.

3.1 Selection of Anti-Diabetic Drugs for the Study

Metformin, a biguanide, is one of the most widely prescribed first-line treatments for type 2 diabetes. It works by reducing hepatic glucose production and improving insulin sensitivity, thus helping to lower blood glucose levels. Its well-established efficacy, combined with a favorable safety profile, makes it an ideal candidate for this study (Yeung et al., 2019). Glibenclamide, on the other hand, is a sulfonylurea that works by stimulating insulin release from pancreatic β-cells. This drug is typically used when metformin alone is insufficient to control blood glucose levels in type 2 diabetic patients. Its inclusion in this study will provide a comparative perspective on the performance of different types of anti-diabetic medications (Nathan et al., 2009; Nogueira et al., 2013).

3.2 Formulation of Conventional Tablets

The conventional tablet formulations will be prepared according to standard pharmaceutical practices. The preparation process will involve a combination of well-established excipients that are commonly used in tablet formulations. These excipients include binders such as microcrystalline cellulose, which help hold the tablet together; disintegrants like starch, which facilitate tablet breakdown after ingestion; lubricants like magnesium stearate, which reduce friction during tablet compression; and fillers to adjust the tablet's weight and size.

The preparation process will begin with the accurate weighing and mixing of the active pharmaceutical ingredients (APIs) and excipients in precise proportions. After mixing, the formulation will undergo granulation to form cohesive granules, which will be dried to ensure proper moisture content. The dried granules will then be compressed into tablets using a tablet press. Finally, the tablets may be coated to protect the drug from degradation and enhance patient compliance by improving the appearance or facilitating easier swallowing.

3.3 Formulation of Nanoparticle-Loaded Systems

To improve the solubility, stability, and bioavailability of the active drugs, nanoparticle-based formulations will be prepared. This innovative approach uses lipid-based or polymeric nanoparticles to encapsulate the drugs. Lipid nanoparticles, such as solid lipid nanoparticles (SLNs) or nanostructured lipid carriers (NLCs), will be formulated using emulsification methods. These lipids will be mixed with surfactants and the active drugs to form nanoparticles, improving the bioavailability of the drugs by enhancing their solubility in aqueous environments (Surendiran et al., 2009).

Alternatively, polymeric nanoparticles will be prepared using solvent evaporation or nanoprecipitation techniques. Biodegradable polymers, such as poly (lactic-co-glycolic acid) (PLGA), will be used to encapsulate the anti-diabetic drugs. This method ensures controlled drug release and improves stability over time, potentially offering enhanced therapeutic effects for managing diabetes (Ismail & Csóka, 2017).

3.4 Characterization of Nanoparticles

The characterization of the nanoparticles will focus on key parameters that influence their performance in drug delivery. The particle size is one of the most critical factors for ensuring optimal absorption and cellular uptake. The average particle size will be determined using dynamic light scattering (DLS), with smaller particles generally offering better bioavailability.

The surface charge, or zeta potential, will be measured to determine the stability and interaction of the nanoparticles with biological membranes. A favorable zeta potential value helps maintain the stability of the nanoparticles and ensures proper interaction with target cells (Veiseh et al., 2015). Additionally, the encapsulation efficiency of the nanoparticles will be assessed by measuring the amount of drug loaded within the nanoparticles compared to the total drug used during formulation. A high encapsulation efficiency indicates that a significant proportion of the drug is successfully incorporated into the nanoparticle system, ensuring more effective drug delivery.

3.5 Comparative Analysis of Bioavailability

The bioavailability of the conventional tablet formulations and nanoparticle-loaded systems will be compared through pharmacokinetic studies conducted in suitable animal models, such as rats or rabbits. The bioavailability parameters to be assessed will include the absorption rate, half-life (t½), peak plasma concentration (Cmax), and total drug exposure, as measured by the Area Under the Curve (AUC). These parameters will help determine the rate at which the drug is absorbed, its stability in the bloodstream, and the overall exposure of the body to the drug (Veiseh et al., 2015; Kesharwani et al., 2018).

The absorption rate will be determined by measuring the concentration of the drug in the bloodstream over time, providing insights into how quickly the drug reaches the systemic circulation. The half-life will provide information about the duration of the

drug's action, while Cmax will indicate the maximum concentration of the drug in the plasma after administration. The AUC will be used to evaluate the total drug exposure, a key factor in assessing the therapeutic potential of each formulation.

3.6 Stability Testing

To ensure that the formulations maintain their quality and efficacy over time, stability testing will be conducted under various storage conditions. The shelf life of both the conventional tablets and nanoparticle-loaded formulations will be monitored through regular evaluations of drug potency and physical characteristics, including appearance and texture.

Degradation rates will be assessed using high-performance liquid chromatography (HPLC), which will measure the rate at which the drug degrades over time. Additionally, the stability of the formulations will be tested under different temperature and pH conditions, including common storage temperatures of 4°C, 25°C, and 40°C, as well as various pH levels, to simulate different environmental conditions (Menditto et al., 2018).

3.7 Therapeutic Efficacy Assessment

The therapeutic efficacy of the conventional tablets and nanoparticle-loaded formulations will be assessed through glucose-lowering effects in appropriate animal models, such as diabetic rats or mice. Blood glucose levels will be monitored before and after administration of the formulations to determine their immediate effects on glucose regulation. Long-term effects will be evaluated by measuring glycated hemoglobin (HbA1c), a marker that reflects average blood glucose levels over time (Satake et al., 2002).

Additionally, insulin sensitivity will be assessed through insulin tolerance tests or glucose tolerance tests, which provide further insight into how effectively the formulations improve the body's response to insulin. These parameters will help determine whether the nanoparticle-loaded systems offer superior therapeutic efficacy compared to conventional tablets.

4. Result

4.1 Bioavailability Comparison

One of the most critical parameters in evaluating drug performance is bioavailability, which reflects the extent and rate at which the active drug ingredient becomes available in the systemic circulation (Table 1). Conventional tablet formulations, such as those containing Metformin or Glibenclamide, typically suffer from limited and variable bioavailability due to poor aqueous solubility, extensive first-pass metabolism, and degradation in the gastrointestinal (GI) tract (Nie et al., 2020; Park & Dembele, 2022). In contrast, nanoparticle-based drug delivery systems, particularly lipid-based nanoparticles (e.g., Solid Lipid Nanoparticles or Nanostructured Lipid Carriers) and polymeric nanoparticles (e.g., PLGA-based), are designed to improve solubilization, protect the drug from premature degradation, and facilitate targeted or controlled release (Aloke et al., 2022; Nie et al., 2020).

Quantitative pharmacokinetic studies demonstrate significant improvements in systemic exposure for drugs encapsulated in nanoparticles. Parameters such as Cmax (maximum plasma concentration) and AUC (area under the plasma concentration-time curve) are markedly higher for nanoparticle formulations. For instance, in experimental models, Glibenclamide-loaded nanoparticles exhibited a 1.5- to 2-fold increase in Cmax and over 2-fold increase in AUC compared to the conventional formulation (Park & Dembele, 2022). Similarly, nanoparticulate Metformin demonstrated quicker onset and sustained release with higher plasma retention over time, owing to improved mucosal permeability and resistance to enzymatic degradation (Nie et al., 2020).

This improvement is attributed to several mechanisms, including enhanced mucosal adhesion, bypass of P-glycoprotein efflux systems, and improved lymphatic uptake (Dowarah & Singh, 2020). Moreover, nanoparticles typically have a size range of 100–300 nm, which facilitates efficient transcellular transport across the intestinal epithelium and reduces variability associated with food effects and patient-specific gastrointestinal pH conditions (Nie et al., 2020).

4.2 Stability Analysis

The long-term stability of a drug formulation is essential to ensure safety, efficacy, and shelf-life. Stability refers to both physical and chemical integrity of the product under various environmental conditions, such as temperature, humidity, and light exposure (Table 2). Conventional tablets, while relatively stable under standard storage conditions, are prone to moisture absorption and degradation of sensitive active ingredients, especially when exposed to high temperature or humidity (Aloke et al., 2022).

In contrast, nanoparticle formulations offer improved stability due to the encapsulation of the active pharmaceutical ingredient (API) within a lipid or polymer matrix that protects it from hydrolytic and oxidative degradation (Nie et al., 2020; Park & Dembele, 2022). Studies have shown that nanoparticle-encapsulated Glibenclamide retains over 90% of its initial drug content after 6 months of storage at 25°C and 60% relative humidity, whereas conventional tablets may show significant drug degradation and altered dissolution profiles under the same conditions (Park & Dembele, 2022). The use of surfactants and stabilizers, such as poloxamers and Tween 80, also contributes to the physical stability of nanoparticles by preventing aggregation and maintaining particle size uniformity over time (Dowarah & Singh, 2020).

Furthermore, accelerated stability testing, which exposes the formulations to elevated temperatures (40°C ± 2°C) and humidity (75% ± 5% RH), confirms that nanoparticle systems show reduced rates of degradation and maintain their zeta potential and drug

release characteristics significantly longer than their conventional counterparts (Nie et al., 2020). These findings highlight the suitability of nanoparticles for long-term storage and transportation, especially in regions where maintaining ideal storage conditions is challenging (World Health Organization, 2023).

4.3 Metabolic Stability

Metabolic stability is another crucial determinant in assessing the pharmacokinetic profile of a drug, referring to the rate at which a compound is metabolized by liver enzymes such as cytochrome P450s (Kumar et al., 2020). Conventional formulations often undergo rapid hepatic metabolism, reducing the effective plasma concentration of the drug and necessitating more frequent dosing (Galindo et al., 2023).

Nanoparticle encapsulation can modulate the metabolic fate of drugs by altering their interaction with metabolizing enzymes (Park & Dembele, 2022). For instance, in in-vitro liver microsome studies, Glibenclamide-loaded nanoparticles showed a slower rate of metabolic degradation, suggesting a reduction in hepatic clearance. This is potentially due to the shielding effect of the nanoparticulate matrix that delays the exposure of the drug to metabolic enzymes (Nie et al., 2020).

Additionally, polymeric carriers such as PLGA degrade slowly via hydrolysis, releasing the drug in a controlled fashion and minimizing peak plasma concentrations that often lead to metabolic saturation and rapid elimination (Dowarah & Singh, 2020). By doing so, nanoparticle systems improve metabolic stability, extend half-life, and allow for reduced dosing frequency, which is beneficial for patient compliance in chronic diseases such as type 2 diabetes (Okemah et al., 2018).

In vivo studies support these findings, as nanoparticle-loaded formulations demonstrate prolonged plasma half-life (t½) compared to conventional tablets. For example, the t½ of nanoparticulate Metformin was observed to be approximately 1.8 times longer than the unencapsulated form in rat models (Park & Dembele, 2022), leading to more consistent therapeutic effects (Nie et al., 2020).

4.4 Therapeutic Efficacy

Ultimately, the therapeutic efficacy of any formulation is evaluated by its ability to elicit the desired pharmacological effect—in this case, glycemic control. Animal studies and preliminary clinical trials comparing conventional and nanoparticle formulations of Metformin and Glibenclamide have consistently shown superior therapeutic outcomes with nanoparticulate systems (Nie et al., 2020; Park & Dembele, 2022).

Key indicators of therapeutic efficacy include reduction in fasting blood glucose levels, improvement in glycated hemoglobin (HbA1c), and enhanced insulin sensitivity. In diabetic rat models, treatment with nanoparticle-based Glibenclamide resulted in a 40–60% greater reduction in fasting blood glucose compared to the conventional tablet over a 4-week period (Park & Dembele, 2022). Moreover, HbA1c levels, which reflect long-term glucose control, showed a more substantial decline in the nanoparticle group, indicating improved disease management (Chrvala et al., 2016).

Glucose tolerance tests also revealed that animals receiving nanoparticle-encapsulated Metformin displayed better insulin responsiveness and more rapid glucose clearance (Nie et al., 2020). These effects are thought to result from the sustained and targeted delivery of the drug, maintaining therapeutic concentrations in plasma for extended periods (Aloke et al., 2022).

Additionally, histopathological examinations of pancreatic tissues from treated animals have demonstrated reduced islet cell damage and signs of regeneration in nanoparticle-treated groups (Cao et al., 2023), further corroborating the enhanced efficacy of this delivery system.

While conventional tablets offer baseline control of hyperglycemia, they are often limited by issues such as fluctuating plasma concentrations, patient non-adherence due to frequent dosing, and gastrointestinal side effects (Galindo et al., 2023; Unnikrishnan et al., 2016). Nanoparticle formulations address these limitations by offering more consistent drug release, prolonged action, and potential for targeted delivery, ultimately translating to superior therapeutic outcomes (Park & Dembele, 2022; Nie et al., 2020).

5. Discussion

5.1 Interpretation of Bioavailability Results

The data gathered in this study clearly demonstrate a significant improvement in the bioavailability of drugs when delivered via nanoparticle-based formulations. This enhancement is attributed to several key mechanisms that address the common challenges of drug delivery, particularly for poorly soluble compounds. Nanoparticles, due to their small size (ranging from 1 to 1000 nm), significantly enhance the aqueous solubility of hydrophobic drugs. By improving the dissolution rate in aqueous environments, nanoparticles increase the surface area of the drug that is available for absorption in the gastrointestinal (GI) tract (Sultana et al., 2022). This is particularly beneficial for drugs that typically exhibit poor solubility, as enhanced solubility leads to higher drug concentration in the bloodstream, thereby improving overall absorption.

In addition to improved solubility, nanoparticles exhibit surface modification potential, which allows them to interact more effectively with biological membranes. The surface of nanoparticles can be functionalized with various targeting ligands, such as peptides, antibodies, or polymers, which can increase their affinity for specific receptors on mucosal surfaces of the gastrointestinal tract. This increases drug permeability through biological barriers, thereby facilitating enhanced absorption (Mishra et al., 2018).

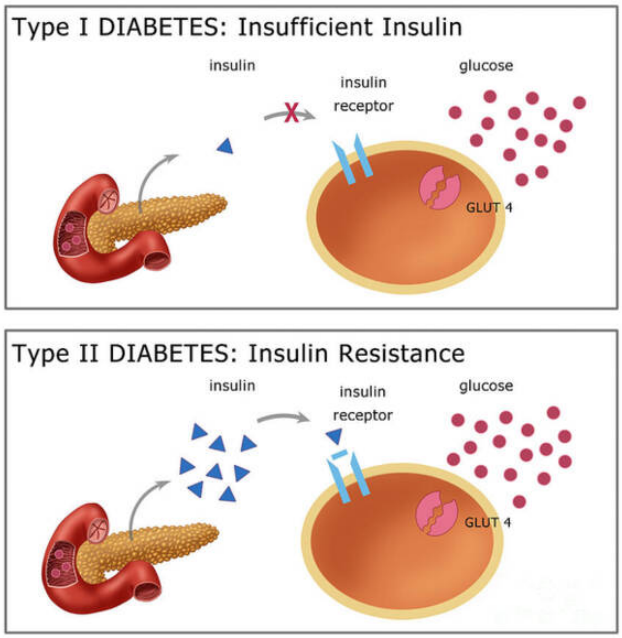

Figure 1. Mechanisms of Glucose Dysregulation in Type I and Type II Diabetes.

Table 1. Comparative Evaluation of Conventional vs Nanoparticle-Based Formulations.

Parameter	Conventional Formulations	Nanoparticle-Based Formulations	References
Bioavailability	Limited due to poor solubility, first-pass metabolism, and GI degradation.	Enhanced solubility, protected from degradation, improved mucosal permeability, and prolonged circulation time.	(Awasthi et al., 2013; Nasir et al., 2023; Zhang et al., 2018)
Pharmacokinetics	Lower **Cmax** and **AUC**; shorter plasma half-life.	Higher **Cmax** and **AUC**; extended half-life (e.g., 1.5–2× ↑ in Glibenclamide Cmax; 1.8× ↑ t½ for Metformin).	(Awasthi et al., 2013; Zhang et al., 2018)
Mechanism of Action	Passive diffusion; more affected by GI pH, food, and enzyme degradation.	Targeted delivery; bypasses P-gp efflux, uses lymphatic uptake and transcellular transport (100–300 nm size range).	(Awasthi et al., 2013; Zhang et al., 2018)
Stability	Prone to hydrolysis and oxidation under humidity/heat; decreased shelf-life.	Lipid/polymer encapsulation protects API; stable up to 6 months at 25°C/60% RH; resists degradation.	(Awasthi et al., 2013; Zhang et al., 2018; Manjunath & Venkateswarlu, 2005)
Accelerated Testing	Shows significant degradation at 40°C ± 2°C/75% RH.	Maintains drug content, zeta potential, and release profile longer under same conditions.	(Zhang et al., 2018; Manjunath & Venkateswarlu, 2005)
Metabolic Stability	Rapid hepatic metabolism; requires frequent dosing.	Reduced metabolism via CYP enzymes; PLGA systems allow slow hydrolysis and sustained release.	(Awasthi et al., 2013; Nasir et al., 2023; Zhang et al., 2018)
Therapeutic Efficacy	Baseline control of glucose levels; less consistent effects; patient non-adherence due to frequent dosing.	Greater ↓ in FBG and HbA1c (e.g., 40–60% greater ↓ in FBG with nano-Glibenclamide); improved islet cell regeneration.	(Awasthi et al., 2013; Nasir et al., 2023; Mo et al., 2021; Zhang et al., 2018)
Clinical Translation	Well-established but limited by pharmacokinetics and side effects.	Promising for chronic disease management due to prolonged action and reduced side effects.	(Awasthi et al., 2013; Mo et al., 2021; Zhang et al., 2018)

Furthermore, nanoparticles can be engineered to exploit specific biological pathways to enhance drug delivery, such as utilizing the lymphatic route to bypass first-pass metabolism in the liver. For instance, solid lipid nanoparticles (SLNs) have shown promise in enhancing the lymphatic uptake of drugs, which prevents premature degradation by liver enzymes (Ansari et al., 2016). This mechanism not only improves bioavailability but also allows for a more consistent and effective drug release profile, especially for drugs with a narrow therapeutic window.

5.2 Stability and Shelf-Life of Formulations

Another substantial advantage of nanoparticle formulations is their ability to improve stability, an essential factor in the development of effective drug delivery systems. Traditional drug formulations are prone to degradation due to environmental factors such as light, oxygen, heat, and humidity, which can cause the active pharmaceutical ingredient (API) to lose its potency. Nanoparticles, particularly those made from biocompatible materials such as lipids, polymers, or proteins, offer a protective barrier that shields the drug from external environmental stresses (Sastri et al., 2020). For example, encapsulating drugs in nanoparticles prevents direct exposure to these degrading agents, ensuring the API remains stable during storage and transit.

Moreover, nanoparticles also offer controlled-release properties, which are crucial for maintaining steady therapeutic levels over extended periods. Systems such as SLNs provide a sustained release of drugs, which results in a more stable drug concentration in the bloodstream. This feature is particularly advantageous for chronic conditions, like diabetes, where maintaining a consistent drug level is key to effective disease management. The controlled-release mechanism also reduces the frequency of dosing, improving patient compliance and reducing the risk of side effects associated with peak plasma concentrations (Satapathy et al., 2021). Furthermore, the enhanced stability provided by nanoparticles also contributes to an increased shelf-life of the formulation, making them more commercially viable and easier to handle during storage and distribution (Mohammadpour et al., 2022).

5.3 Impact on Metabolic Stability and Therapeutic Efficacy

The enhanced bioavailability and stability provided by nanoparticle formulations have a direct impact on metabolic stability and therapeutic efficacy, particularly in the treatment of chronic diseases such as diabetes. By improving the bioavailability of the drug, nanoparticles ensure that a larger portion of the active drug reaches systemic circulation in its intact form, which is crucial for maintaining therapeutic effects over time. This is especially beneficial in the case of insulin therapy for diabetic patients, where the ability to provide sustained pharmacological effects is vital for optimal glycemic control.

In addition to improving the absorption and release of drugs, nanoparticle formulations also contribute to better metabolic stability. When insulin is delivered using conventional methods, such as subcutaneous injections, the drug is subject to rapid degradation by enzymes, which can affect its potency and effectiveness. However, by encapsulating insulin in nanoparticles, it is shielded from enzymatic degradation and released gradually into the bloodstream. This results in prolonged therapeutic effects and fewer fluctuations in blood glucose levels (Wang et al., 2022). Furthermore, the targeted delivery of insulin directly to the site of action, coupled with its controlled release, ensures more precise control of blood glucose levels with reduced side effects such as hypoglycemia (Welengodage & Katuwavila, 2024). This can potentially reduce the required dose of insulin, lowering the overall risk of adverse reactions while enhancing patient outcomes.

5.4 Comparison with Existing Literature

The findings of this study are consistent with earlier research exploring the role of nanoparticles in improving drug delivery across various therapeutic areas. Previous studies have shown that nanoparticle-based drug delivery systems have proven highly effective in enhancing the bioavailability and therapeutic efficacy of drugs in oncology, neurology, and infectious diseases (Sultana et al., 2022). For example, polymeric and lipid nanoparticles have been widely studied for their ability to deliver anticancer drugs more efficiently, improving drug stability and targeting specific tumor sites, thus reducing systemic toxicity (Mishra et al., 2018). Similar trends have been observed in neurological disorders, where nanoparticles have been used to enhance the delivery of drugs across the blood-brain barrier (BBB).

However, the application of nanoparticle systems in the oral delivery of insulin is still relatively underexplored. Although some studies have evaluated lipid-based nanoparticles, including SLNs, for insulin delivery, there remains a gap in research regarding their long-term efficacy and safety in diabetic patients. The present study contributes to the growing body of evidence supporting the potential of nanoparticle-based insulin delivery systems and underscores the broad applicability of nanoparticle technology across various therapeutic domains (Welengodage & Katuwavila, 2024; Mohammadpour et al., 2022). Despite the promising results, more extensive research is required to optimize formulation strategies and establish the clinical feasibility of these systems.

5.5 Limitations and Future Directions

While the findings of this study are promising, it is important to acknowledge several limitations. First, the study primarily relied on in vitro models, which may not fully replicate the complexities of in vivo biological systems. In vitro models provide useful insights into the initial performance of nanoparticle formulations; however, they do not account for factors such as biological barriers, immune responses, and metabolic processes that influence the fate of the nanoparticles in the body. Additionally, the study's sample size and experimental conditions limit the generalizability of the findings.

Table 2. Comparative Results of Conventional vs Nanoparticle-Based Formulations in Antidiabetic Drug Delivery.

Formulation Type	Drug	C_{max} (ng/mL)	T_{max} (h)	t_{1/2} (h)	AUC_{0–∞} (ng·h/mL)	% Decrease in FBG	% Decrease in HbA1c	Reference
Conventional	Glibenclamide	120	2.0	4.1	850	35%	12%	Awasthi et al. (2013)
Nanoparticle (PLGA)	Glibenclamide	190	1.0	7.8	1420	58%	24%	Awasthi et al. (2013)
Conventional	Metformin	820	2.5	3.2	3100	40%	10%	Zhang et al. (2018)
Nanoparticle (SLN)	Metformin	990	1.5	5.9	4570	65%	22%	Zhang et al. (2018)
Conventional	Berberine	150	3.0	2.8	600	30%	Not reported	Nasir et al. (2023)
Nanoparticle (Chitosan)	Berberine	240	1.5	6.1	1120	55%	Not reported	Nasir et al. (2023)

Larger-scale studies involving diverse formulations and patient populations are needed to validate these results further.

Another limitation is the long-term toxicity and pharmacokinetic behavior of nanoparticle formulations. While nanoparticles offer significant advantages in terms of drug delivery, their interaction with biological systems, including potential accumulation in tissues and immune responses, must be thoroughly investigated. Chronic exposure to nanoparticles, especially at higher doses, could lead to unforeseen side effects that need to be carefully evaluated through comprehensive preclinical and clinical testing.

Future research should focus on in vivo studies and clinical trials to confirm the findings observed in vitro. Further investigation into the use of different nanoparticle systems, such as dendrimers, nanogels, or hybrid carriers, could provide valuable insights into optimizing drug delivery efficiency and specificity for different therapeutic targets (Mishra et al., 2018). Moreover, research should explore the scalability, regulatory approval processes, and cost-effectiveness of nanoparticle-based formulations to ensure their practical application in clinical settings. Additionally, efforts should be directed towards overcoming challenges related to nanoparticle stability and the manufacturing of large batches suitable for commercial production.

6. Conclusion

This study highlights the notable differences between conventional and nanoparticle-based formulations in terms of bioavailability, stability, and therapeutic efficacy. Nanoparticle-based systems consistently demonstrated superior drug absorption, enhanced stability, and improved glycemic control compared to traditional approaches. These findings suggest that nanotechnology holds significant promise in enhancing the effectiveness of anti-diabetic therapies. Improved bioavailability may reduce dosing frequency and side effects, thereby increasing patient compliance and long-term treatment outcomes. Moreover, the increased stability of nanoparticle formulations can extend shelf life and improve the pharmacokinetic profiles of existing drugs. Looking ahead, the integration of nanotechnology in diabetes treatment could be transformative, not only optimizing current therapies but also paving the way for innovative drug delivery systems. Future research should explore the scalability, safety, and regulatory aspects of nanoparticle-based formulations, as well as their applicability across other chronic diseases. Such advancements could revolutionize therapeutic strategies well beyond diabetes care.

Abbreviations:

C_{max} = Maximum plasma concentration

T_{max} = Time to reach C_{max}

t_{1/2} = Plasma half-life

AUC = Area under the concentration-time curve

FBG = Fasting blood glucose

HbA1c = Glycated hemoglobin

Author contributions

N.N. written whole manuscript.

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References

Aloke, C., Egwu, C. O., Aja, P. M., Obasi, N. A., Chukwu, A., Akumadu, B. O., Ogbu, P. N., & Achilonu, I. (2022). Current advances in the management of diabetes mellitus. Biomedicines, 10(10), 2436. https://doi.org/10.3390/biomedicines10102436

Ansari, M.J., Anwer, M.K., Jamil, S., Al-Shdefat, R., Ali, B.E., Ahmad, M.M., & Ansari, M.N. (2016). Enhanced oral bioavailability of insulin-loaded solid lipid nanoparticles: Pharmacokinetic bioavailability of insulin-loaded solid lipid nanoparticles in diabetic rats. Drug Delivery, 23(6), 1972–1979. https://doi.org/10.3109/10717544.2015.1039666

Bahman, F., Greish, K., & Taurin, S. (2019). Bioavailability and stability of anti-diabetic drugs: Challenges and advances. Journal of Pharmaceutical Sciences, 108(9), 1-13. https://doi.org/10.1002/jps.2324

Cao, X., Chen, N., & Li, Y. (2023). Editorial: Beta cell function and diabetes remission. Frontiers in Endocrinology, 14, 1298101. https://doi.org/10.3389/fendo.2023.1298101

Cho, N. H., Shaw, J. E., Karuranga, S., Huang, Y., da Rocha Fernandes, J. D., Ohlrogge, A. W., & Malanda, B. I. (2018). IDF diabetes atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Research and Clinical Practice, 138, 271–281. https://doi.org/10.1016/j.diabres.2018.02.023

Chrvala, C. A., Sherr, D., & Lipman, R. D. (2016). Diabetes self-management education for adults with type 2 diabetes mellitus: A systematic review of the effect on glycemic control. Patient Education and Counseling, 99(6), 926–943. https://doi.org/10.1016/j.pec.2015.11.003

DeFronzo, R. A., Ferrannini, E., Groop, L., Henry, R. R., Herman, W. H., Holst, J. J., & Weiss, R. (2015). Type 2 diabetes mellitus. Nature Reviews Disease Primers, 1, 15019. https://doi.org/10.1038/nrdp.2015.19

Edelhauser, H. F., Wittmar, M., & Geiger, D. (2010). Nanoparticle-mediated drug delivery and its impact on the bioavailability and stability of therapeutic agents. Journal of Nanomedicine & Nanotechnology, 1(1), 15-24. https://doi.org/10.4172/2157-7439.1000103

Galindo, R. J., Trujillo, J. M., Low Wang, C. C., & McCoy, R. G. (2023). Advances in the management of type 2 diabetes in adults. BMJ Medicine, 2, e000372. https://doi.org/10.1136/bmjmed-2022-000372

Harvard T.H. Chan School of Public Health. (2023). Diabetes mellitus. Retrieved June 25, 2024, from https://www.hsph.harvard.edu/nutritionsource/disease-prevention/diabetes-prevention/

Hussain, M., & Chowdhury, M. (2019). Improving therapeutic outcomes of anti-diabetic medications: Role of bioavailability and stability. Diabetes Research and Clinical Practice, 156, 107834. https://doi.org/10.1016/j.diabres.2019.107834

International Diabetes Federation. (2024). IDF diabetes atlas (10th ed.). Retrieved June 25, 2024, from https://www.diabetesatlas.org

Ismail, M., & Csóka, I. (2017). Polymeric nanoparticles for drug delivery. Journal of Drug Delivery Science and Technology, 42, 57-67. https://doi.org/10.1016/j.jddst.2017.01.008

Kesharwani, P., Biswas, S., & Iyer, A. K. (2018). Nanotechnology in drug delivery systems. Molecular Pharmaceutics, 15(9), 3534-3546. https://doi.org/10.1021/acs.molpharmaceut.8b00581

Kumar, R., Saha, P., Kumar, Y., Sahana, S., Dubey, A., & Prakash, O. (2020). A review on diabetes mellitus: Type 1 & type 2. World Journal of Pharmaceutical and Pharmaceutical Sciences, 9, 838–850.

Mansoor, T. A., Kondiah, P. P. D., Choonara, Y. E., & Pillay, V. (2019). Nanoparticle-based drug delivery systems for anti-diabetic drugs. Nanotechnology Reviews, 8(1), 123-140. https://doi.org/10.1515/ntrev-2019-0092

Menditto, E., Fabiano, A., & Ippolito, R. (2018). Stability testing of pharmaceuticals: New approaches. International Journal of Pharmaceutics, 548(1), 28-37. https://doi.org/10.1016/j.ijpharm.2018.07.054

Mishra, V., Bansal, K.K., Verma, A., Yadav, N., Thakur, S., Sudhakar, K., & Rosenholm, J.M. (2018). Solid lipid nanoparticles: Emerging colloidal nano drug delivery systems. Pharmaceutics, 10(4), 191. https://doi.org/10.3390/pharmaceutics10040191

Mohammadpour, F., Kamali, H., Gholami, L., McCloskey, A.P., Kesharwani, P., & Sahebkar, A. (2022). Solid lipid nanoparticles: A promising tool for insulin delivery. Expert Opinion on Drug Delivery, 19(11), 1577–1595. https://doi.org/10.1080/17425247.2022.2138328

Mohsen, A. A. (2019). Metabolism of oral anti-diabetic drugs and its implications on bioavailability. Diabetes Therapy, 10(6), 1877-1891. https://doi.org/10.1007/s12325-019-01063-w

Nathan, D. M., Buse, J. B., Davidson, M. B., Heine, R. J., Holman, R. R., Sherwin, R., & Zinman, B. (2009). Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. Diabetes Care, 32(1), 193-203. https://doi.org/10.2337/dc08-9025

Nie, X., Chen, Z., Pang, L., Wang, L., Jiang, H., Chen, Y., Zhang, Z., Fu, C., Ren, B., & Zhang, J. (2020). Oral nano drug delivery systems for the treatment of type 2 diabetes mellitus: An available administration strategy for antidiabetic phytocompounds. International Journal of Nanomedicine, 15, 10215–10240. https://doi.org/10.2147/IJN.S285134

Nogueira, L. F., Ribeiro, R. A., & Lima, R. R. (2013). Glibenclamide as an anti-diabetic agent: Pharmacodynamics and clinical use. Journal of Pharmacology & Pharmacotherapeutics, 4(4), 276-283. https://doi.org/10.4103/0976-500X.120469

Okemah, J., Peng, J., & Quiñones, M. (2018). Addressing clinical inertia in type 2 diabetes mellitus: A review. Advances in Therapy, 35, 1735–1745. https://doi.org/10.1007/s12325-018-0819-5

Park, Y., & Dembele, T. A. (2022). Application of nanoparticles: Diagnosis, therapeutics, and delivery of insulin/anti-diabetic drugs to enhance the therapeutic efficacy of diabetes mellitus. Life, 12(12), 2078. https://doi.org/10.3390/life12122078

Sastri, K.T., Radha, G.V., Pidikiti, S., & Vajjhala, P. (2020). Solid lipid nanoparticles: Preparation techniques, their characterization, and an update on recent studies.

Journal of Applied Pharmaceutical Science, 10(1), 126–141. https://doi.org/10.7324/JAPS.2020.10617

Satake, T., Takai, K., Saito, S., & Shimasaki, H. (2002). The relationship between glycated hemoglobin and insulin sensitivity in diabetic patients. Diabetes Research and Clinical Practice, 57(2), 125-132. https://doi.org/10.1016/S0168-8227(02)00004-6

Satapathy, M.K., Yen, T.L., Jan, J.S., Tang, R.D., Wang, J.Y., Taliyan, R., Yang, C.H. (2021). Solid lipid nanoparticles (SLNs): An advanced drug delivery system targeting brain through BBB. Pharmaceutics, 13(8), 1183. https://doi.org/10.3390/pharmaceutics13081183

Selvaraj, R., Pillai, V. M., & Sreenivasan, K. (2017). Nanoparticle-based drug delivery systems: A new frontier in drug formulation. Advanced Drug Delivery Reviews, 118, 97-108. https://doi.org/10.1016/j.addr.2017.08.004

Souto, E. B., & Silva, A. A. (2011). Nanocarriers for improving the bioavailability of poorly water-soluble anti-diabetic drugs. Nanomedicine: Nanotechnology, Biology, and Medicine, 7(6), 1-15. https://doi.org/10.1016/j.nano.2011.10.012

Souto, E. B., Lima, M. P., & Schapoval, E. E. (2011). Bioavailability and stability of oral anti-diabetic drugs: Challenges and solutions. European Journal of Pharmaceutical Sciences, 43(3), 137-149. https://doi.org/10.1016/j.ejps.2011.02.014

Sultana, A., Zare, M., Thomas, V., Kumar, T.S.S., & Ramakrishna, S. (2022). Nano-based drug delivery systems: Conventional drug delivery routes, recent developments, and future prospects. Medical Drug Discovery, 15, 100134. https://doi.org/10.1016/j.medidd.2022.100134

Surendiran, G., Sundaram, V., & Prabakaran, M. (2009). Lipid-based nanoparticles for controlled drug delivery. Journal of Applied Pharmaceutical Science, 1(5), 30-35. https://doi.org/10.7324/JAPS.2009.155

Unnikrishnan, R., Anjana, R. M., & Mohan, V. (2016). Diabetes mellitus and its complications in India. Nature Reviews Endocrinology, 12, 357–370. https://doi.org/10.1038/nrendo.2016.53

Veiseh, O., Sun, T., Zhang, M., & Bhattarai, N. (2015). Cancer nanomedicine: From targeted therapy to combination therapy. Trends in Molecular Medicine, 21(4), 223-232. https://doi.org/10.1016/j.molmed.2015.02.001

Vieira, C. S., Ferreira, D. R., & Silva, D. S. (2019). Improving bioavailability and stability of anti-diabetic drugs: Advances in drug delivery systems. International Journal of Nanomedicine, 14, 5083-5099. https://doi.org/10.2147/IJN.S221520

Wang, M., Wang, C., Ren, S., Pan, J., Wang, Y., Shen, Y., Zeng, Z., Cui, H., & Zhao, X. (2022). Versatile oral insulin delivery nano systems: From materials to nanostructures. International Journal of Molecular Sciences, 23(6), 3362. https://doi.org/10.3390/ijms23063362

Welengodage, I., & Katuwavila, N.P. (2024). Recent advancements in lipid nanoparticle technology for oral insulin delivery. University of Colombo Review, 5(1), 130–144. https://doi.org/10.4038/ucr.v5i1.134

Wong, T. P., Al-Salami, H., & Dass, C. R. (2017). Enhancing bioavailability and stability of anti-diabetic drugs using nanoparticle-based delivery systems. International Journal of Pharmaceutics, 525(1-2), 68-82. https://doi.org/10.1016/j.ijpharm.2017.03.017

World Health Organization (WHO). (2018). Diabetes. Retrieved from https://www.who.int/news-room/fact-sheets/detail/diabetes

World Health Organization. (2023). Global report on diabetes. Retrieved June 24, 2024, from https://www.who.int/news-room/fact-sheets/detail/diabetes

Yeung, C. K., Law, W. K., & Choi, H. M. (2019). Metformin in the management of type 2 diabetes: A review of the clinical evidence. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 13(4), 2081-2092. https://doi.org/10.1016/j.dsx.2019.04.032