REVIEW ARTICLE

Antidiabetic Drug-loaded Solid Lipid Nanoparticle and Its Importance in Drug Delivery

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ABSTRACT

The global health challenge of diabetes mellitus continues to escalate, affecting millions of people worldwide. Managing this chronic condition necessitates lifelong treatment to control hyperglycemia and prevent complications. The delivery of antidiabetic medications can be improved by solid lipid nanoparticles (SLNs). This review provides an overview of current research on antidiabetic-loaded SLNs, summarizing their efficacy, safety, and challenges. Various antidiabetic agents, including insulin, metformin, sulfonylureas, and GLP-1 agonists, have been successfully encapsulated into SLNs, offering improved pharmacokinetic profiles and therapeutic outcomes. Despite their potential, optimization of SLN formulations, scale-up challenges, and translation to clinical practice remain areas requiring further investigation. With ongoing advancements in nanotechnology and drug delivery, antidiabetic-loaded SLNs hold promise for revolutionizing diabetes therapy and improving patient care.

Keywords: Solid lipid nanoparticles, Antidiabetic, International Diabetes Federation, Insulin therapy, Nanocarrier.

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INTRODUCTION

Globally, diabetes mellitus is becoming an increasingly serious health concern due to its rising prevalence. In 2019, there were approximately 463 million diagnosed diabetes cases among adults aged 20 to 79, according to the International Diabetes Federation (IDF). According to projections, the number is expected to increase to 700 million by 2045.[1] The management of diabetes poses multifaceted challenges due to its chronic nature, diverse complications, and the need for lifelong treatment. Achieving optimal glycemic control to prevent long-term complications remains a primary goal in diabetes management, yet it often proves elusive due to various factors such as medication adherence, lifestyle factors, and individual patient variability.[2]

In addition to limitations in bioavailability and frequent dosing, the traditional methods of treating diabetes involve insulin therapy and oral medications. In recent years, however, advances in drug delivery have provided innovative solutions that aim to improve antidiabetic medication effectiveness and safety. Solid lipid nanoparticles (SLNs) have emerged as promising drug delivery systems, offering unique advantages over conventional formulations.

These colloidal carriers, which range from 10 to 1000 nanometers in size, are composed of biocompatible lipids. The potential for them to overcome drug delivery limitations associated with conventional systems has caused significant interest in recent years.[3] It is possible to encapsulate both hydrophilic and hydrophobic drugs with SLNs, due to their high loading capacity, controlled release kinetics, enhanced stability, and their ability to load both hydrophilic and hydrophobic drugs. In addition, SLNs can make drugs more soluble, keep them from degrading, and deliver them directly to specific tissues or cells.[4]

Exploring the application of SLNs in delivering antidiabetic drugs holds immense promise in addressing the challenges associated with diabetes management. By encapsulating antidiabetic agents into SLNs, it is possible to enhance their bioavailability, prolong their action, and minimize adverse effects. Furthermore, SLNs offer the potential for targeted delivery to sites of action, such as pancreatic islet cells or insulin-sensitive tissues, thereby maximizing therapeutic efficacy while minimizing systemic side effects.

In this context, this review aims to explore the significance of utilizing SLNs as drug delivery systems for antidiabetic medications. By providing an overview of the global burden of diabetes, the challenges in its management, and the potential of SLNs in improving drug delivery, this review seeks to

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highlight the importance of ongoing research in this field and its implications for diabetes therapy.

Solid Lipid Nanoparticles: An Overview

Definition and characteristics of SLN

A SLN is a colloidal nanocarrier composed of solid lipids at room and body temperatures. Surfactants or polymers stabilize the solid lipid core, ranging in size from 10 to 1000 nm.[5] SLNs offer several unique characteristics:

- *Biocompatibility*

Lipid materials used in SLNs are generally bio-compatible as well as bio-degradable, reducing adverse reaction risks.

- *High drug loading capacity*

SLNs can encapsulate hydrophobic as well as hydrophilic drugs due to their lipophilic core, allowing for efficient drug loading.

- *Controlled drug release*

An SLN provides controlled release kinetics, providing sustained drug release over a longer period of time, resulting in improved therapeutic efficacy.

- *Enhanced stability*

Encapsulation within SLNs protects drugs from degradation by enzymes or chemical reactions, enhancing their stability and shelf-life.

Advantages of SLNs over conventional delivery system

SLN has more advantages than conventional drug delivery systems, including:

- *Improved bioavailability*

By increasing the solubility and facilitation of absorption, SLNs can increase the bioavailability of poorly soluble drugs.

- *Targeted drug delivery*

It is possible to design SLNs that target specific tissues and cells in order to reduce side effects on the system and improve therapeutic outcomes.

- *Reduced toxicity*

The biocompatible nature of SLNs reduces the risk of toxicity and adverse reactions compared to other delivery systems.

- *Versatility*

The versatility of SLNs makes them ideal carriers for the delivery of various therapeutic agents, such as small molecules, peptides, and nucleic acids.

Mechanisms of drug encapsulation and release from SLNs

The encapsulation of drugs into SLNs can occur through various mechanisms, including:

- *Solubilization*

Hydrophobic drugs are solubilized within the lipid core of SLNs due to their lipophilic nature.

- *Entrapment*

Hydrophilic drugs are entrapped within the aqueous phase of SLNs or adsorbed onto the surface of lipid nanoparticles.

- *Ion pairing*

Ionic or charged drugs can be complexed with lipids or surfactants to enhance their encapsulation into SLNs.

- *Covalent bonding*

Drugs can be covalently conjugated to lipid molecules, facilitating their incorporation into SLNs.

The release of drugs from SLNs occurs through diffusion, erosion, or a combination of both mechanisms. Factors such as lipid composition, particle size, and surface properties influence the release kinetics of drugs from SLNs.[6]

Antidiabetic drugs and their encapsulation into SLNs

The encapsulation of antidiabetic drugs into SLNs offers potential advantages in improving their therapeutic efficacy and reducing side effects. Various antidiabetic agents, including insulin, metformin, sulfonylureas, and GLP-1 agonists, have been successfully encapsulated into SLNs.[7]

For example, insulin, a peptide hormone used in the treatment of diabetes, has poor oral bioavailability due to enzymatic degradation and poor membrane permeability. Encapsulation of insulin into SLNs can protect it from enzymatic degradation, prolong its circulation time, and enhance its tissue targeting, thereby improving its therapeutic efficacy.[8]

Metformin, a first-line oral antidiabetic drug, can benefit from SLN encapsulation to improve its bioavailability and reduce gastrointestinal side effects. Sulfonylureas, such as glibenclamide and glimepiride, can be formulated into SLNs to improve their pharmacokinetic profile and reduce the risk of hypoglycemia. GLP-1 agonists, such as exenatide and liraglutide, can be delivered *via* SLNs to provide controlled release kinetics and targeted delivery to pancreatic islet cells.[9]

In summary, the encapsulation of antidiabetic drugs into SLNs offers promising opportunities to improve diabetes therapy by enhancing drug stability, bioavailability, and targeted delivery. Further research in this area holds the potential to revolutionize the treatment of diabetes and improve patient outcomes.

Insulin

Challenges associated with insulin therapy

Individuals diagnosed with type 1 diabetes as well as those with advanced type 2 diabetes, experience significant benefits from insulin therapy. However, traditional insulin therapy has several challenges, including:

Poor pharmacokinetics

Insulin has a short half-life and rapid clearance from the bloodstream, necessitating frequent injections to maintain therapeutic levels.

Immunogenicity

Frequent administration of exogenous insulin can lead to the development of anti-insulin antibodies, potentially reducing its effectiveness over time.

Hypoglycemia risk

Achieving tight glycemic control with insulin therapy increases the risk of hypoglycemia, which can be life-threatening.

Patient adherence

Multiple daily injections and the need for strict adherence to dosing schedules can be burdensome for patients, leading to poor compliance.

Benefits of encapsulating Insulin into SLNs

Encapsulating insulin into SLNs offers several advantages for overcoming these challenges:

Improved stability

SLNs provide a protective barrier around insulin molecules, shielding them from enzymatic degradation and proteolysis, thus enhancing their stability in physiological conditions.[10]

Prolonged action

It was possible to prolong the pharmacokinetics of insulin when it is released from SLNs, thus reducing the frequency of administration and enhancing patient compliance.[11]

Reduced immunogenicity

SLNs can minimize the immunogenicity of insulin by altering its presentation to the immune system and reducing antibody formation.[12]

Targeted delivery

SLNs can be engineered to selectively target a specific tissue or cell, such as pancreatic beta cells, thereby increasing insulin's efficacy without causing substantial systemic effects.[13]

Metformin

Metformin as a first-line diabetes treatment

The effectiveness, safety profile, and affordability of metformin make it one of the most prevalent choices for treating type 2 diabetes. Glucose production was decreased in the liver, peripheral glucose uptake was enhanced, and insulin sensitivity is enhanced.[14]

Enhancement of metformin bioavailability and tolerability through SLN encapsulation

Encapsulating metformin into SLNs can address several limitations associated with its oral administration:

- *Improved bioavailability*

SLNs can enhance the bioavailability of metformin by increasing its solubility and protecting it from degradation in the gastrointestinal tract.[15]

- *Controlled release*

With SLNs, metformin can be sustained for longer periods of time, leading to a reduction in dosing frequency and prolongation of therapeutic effects.[16]

Reduced gastrointestinal side effects

SLNs can minimize the gastrointestinal side effects commonly associated with metformin, such as diarrhea and abdominal discomfort, by reducing its direct contact with the gastrointestinal mucosa.[17]

Sulfonylureas

Mechanism of action and clinical relevance of sulfonylurea drugs

ATP-sensitive potassium channels in pancreatic beta cells stimulate insulin secretion by sulphonylureas, a class of oral antidiabetic medications. Their effectiveness in lowering blood glucose levels explains their widespread use in managing type 2 diabetes.[18]

Advantages of delivering sulfonylureas via SLNs

Encapsulation of sulfonylureas into SLNs offers several potential advantages:

- *Improved pharmacokinetics*

SLNs can enhance the pharmacokinetic profile of sulfonylureas by improving their solubility, bioavailability, and tissue distribution.[19]

- *Reduced side effects*

SLNs can mitigate the risk of hypoglycemia associated with sulfonylurea therapy by providing controlled release kinetics, thereby minimizing fluctuations in plasma drug concentrations.[20]

- *Enhanced tissue targeting*

SLNs can be designed to target specific tissues or organs, such as the pancreas, thereby optimizing drug delivery and minimizing off-target effects.[21]

GLP-1 Agonists

Significance of GLP-1 agonists in diabetes management

Diabetes type 2 is managed by injectable medications called glucagon-like peptide-1 (GLP-1) agonists. Natural GLP-1 mimics the functions of insulin secretion, glucagon secretion, and fullness by stimulating insulin secretion and inhibiting glucagon secretion.[22]

Utilization of SLNs for controlled release and targeted delivery of GLP-1 agonists.

Encapsulating GLP-1 agonists into SLNs offers several potential benefits:

- *Controlled release*

SLNs can provide sustained release of GLP-1 agonists, prolonging their pharmacological effects and reducing the frequency of administration.[23]

- *Enhanced stability*

SLNs can protect GLP-1 agonists from enzymatic degradation and proteolysis, improving their stability in biological fluids.[24]

- *Targeted delivery*

SLNs can be engineered to target specific cells or tissues involved in glucose homeostasis, such as pancreatic islet cells or intestinal epithelial cells, thereby maximizing therapeutic efficacy while minimizing systemic side effects.[25]

Importance of Antidiabetic Drug Loaded SLNs in Drug Delivery

Enhanced dioavailability

SLNs play a crucial role in improving the bioavailability of antidiabetic drugs, thereby enhancing their therapeutic outcomes. The encapsulation of antidiabetic agents into SLNs can lead to improved bioavailability through various mechanisms.

Enhanced solubility

By incorporating them into the lipid matrix, SLNs can solubilize poorly water-soluble antidiabetic drugs, such as certain sulfonylureas or GLP-1 agonists. This increased solubility enhances drug absorption and systemic availability.[26]

Protection from degradation

Encapsulation in SLNs protects antidiabetic drugs against enzyme degradation and metabolism, especially in the gastrointestinal tract. Consequently, a higher proportion of the drug reaches the systemic circulation intact, increasing its bioavailability[27].

Enhanced permeability

SLNs can improve the permeability of antidiabetic drugs across biological barriers, such as the intestinal epithelium or the blood-brain barrier (in the case of centrally acting agents). By enhancing drug permeation, SLNs contribute to improved systemic absorption and bioavailability.[28]

Overall, the enhanced bioavailability achieved through SLN encapsulation translates into improved therapeutic efficacy and better glycemic control in diabetic patients.

Targeted Delivery

SLNs offer unique advantages for targeted delivery of antidiabetic drugs to specific tissues or cells involved in diabetes pathophysiology. Modifying the surface properties of SLNs or incorporating targeting ligands can achieve tissue-specific drug delivery, minimize off-target effects, and enhance therapeutic efficacy.[29]

For example, SLNs can be engineered to target pancreatic β-cells, where insulin secretion occurs, or adipocytes, which play a crucial role in insulin sensitivity. Targeted delivery of antidiabetic drugs to these tissues enhances drug accumulation at the site of action, maximizing therapeutic outcomes while minimizing systemic exposure and potential side effects.[30]

Additionally, SLNs can be designed for targeted delivery to sites of diabetic complications, such as the kidneys (for diabetic nephropathy) or the retina (for diabetic retinopathy). This targeted approach allows for the delivery of therapeutic agents directly to the affected tissues, improving treatment efficacy and reducing systemic toxicity.[31]

Prolonged Action

SLNs are capable of sustained drug release, thus prolonging the therapeutic effects of drugs and reducing the frequency of dosing. As antidiabetic drugs are encapsulated within SLNs, controlled release kinetics becomes feasible, allowing therapeutic drug concentrations to be sustained for longer periods of time in the bloodstream.[32]

The sustained release of antidiabetic drugs from SLNs offers several benefits:

Reduced Fluctuations in *Blood Glucose Levels*: Sustained drug release ensures more stable blood glucose levels, minimizing the risk of hypoglycemia and hyperglycemia.

Improved Patient Adherence: Reduced dosing frequency due to prolonged drug action enhances patient adherence to treatment regimens, leading to better glycemic control and overall treatment outcomes.

Enhanced Therapeutic Efficacy: Prolonged drug action allows for continuous suppression of hyperglycemia, leading to better glycemic control and potentially reducing the risk of long-term diabetic complications[33].

Overall, the prolonged action achieved through SLN-mediated drug delivery contributes to improved treatment outcomes and better quality of life for diabetic patients.

Improved Stability

Encapsulation of antidiabetic drugs into SLNs provides protection against degradation and metabolism, thereby enhancing their stability and shelf-life. The lipid matrix of SLNs acts as a barrier, shielding the encapsulated drugs from environmental factors such as pH changes, enzymatic degradation, and oxidative stress.[34]

This improved stability offers several advantages

- *Extended shelf-life*

Antidiabetic drugs encapsulated within SLNs exhibit improved stability during storage, reducing the need for frequent formulation adjustments and enhancing product shelf-life.

- *Enhanced formulation compatibility*

SLN encapsulation can improve the compatibility of antidiabetic drugs with excipients and formulation components, reducing the risk of degradation or interaction during formulation and storage.

- *Preservation of therapeutic efficacy*

By protecting antidiabetic drugs from degradation, SLNs ensure that the drugs retain their pharmacological activity and efficacy throughout the shelf-life of the formulation.[35]

Overall, the improved stability achieved through SLN encapsulation enhances the quality and reliability of antidiabetic drug formulations, ensuring consistent therapeutic outcomes for diabetic patients.

Challenges and Future Perspectives

Identification of challenges in the development and translation of antidiabetic drug-loaded SLNs

Despite the promising potential of antidiabetic drug-loaded SLNs, several challenges exist in their development and translation into clinical practice:

Formulation optimization

Achieving optimal formulation parameters, such as lipid

composition, particle size, and drug loading capacity, is essential for maximizing the therapeutic efficacy of antidiabetic drug-loaded SLNs. However, formulating SLNs with suitable properties while maintaining stability and scalability can be challenging.[36]

Stability issues

SLNs may encounter stability issues during storage and administration, including particle aggregation, drug leakage, and lipid oxidation. Addressing these stability concerns is crucial to ensure the reliability and shelf-life of antidiabetic drug-loaded SLN formulations.[37]

Scale-up and manufacturing challenges

Scaling up the production of SLNs from laboratory to industrial scale poses reproducibility, cost-effectiveness, and regulatory compliance challenges. Developing scalable manufacturing processes for antidiabetic drug-loaded SLNs is essential for their widespread commercialization and clinical adoption.[38]

Pharmacokinetic variability

The pharmacokinetics, efficacy, and distribution of antidiabetic drugs loaded in SLNs may change depending on the individual's absorption, distribution, metabolism, and excretion (ADME). Optimizing dosing regimens and achieving consistent therapeutic outcomes depend on understanding and addressing these pharmacokinetic factors.[39]

Opportunities for Future Research

Despite the challenges, there are several opportunities for future research to advance the development and translation of antidiabetic drug-loaded SLNs.

Optimization of formulation parameters

Further research is needed to optimize the formulation parameters of antidiabetic drug-loaded SLNs, including lipid composition, surfactant selection, and manufacturing techniques. Utilizing advanced characterization methods and design of experiments (DOE) approaches can facilitate the development of robust SLN formulations with enhanced therapeutic efficacy.[40]

Scale-up and manufacturing optimization

Developing scalable and cost-effective manufacturing processes for antidiabetic drug-loaded SLNs is essential for their commercialization. Research efforts should focus on optimizing production techniques, such as high-pressure homogenization, solvent evaporation, or microfluidics, to ensure reproducibility and regulatory compliance.[41]

Preclinical and clinical studies

Conducting preclinical studies to evaluate the pharmacokinetics, pharmacodynamics, and safety of antidiabetic drug-loaded SLNs is crucial for advancing their clinical translation. Subsequent clinical trials are needed to assess the efficacy and tolerability of SLN formulations in diabetic patients, ultimately leading to regulatory approval and market availability.[42]

Personalized medicine approaches

Incorporating personalized medicine approaches, such as pharmacogenomics and patient stratification based on disease phenotype, can optimize the therapeutic outcomes of antidiabetic drug-loaded SLNs. Tailoring SLN formulations to individual patient characteristics and treatment goals may improve treatment adherence and efficacy.[43]

CONCLUSION

In conclusion, antidiabetic drug-loaded SLNs are promising to improve diabetes therapy by enhancing drug stability, bioavailability, and targeted delivery. Despite existing challenges in formulation optimization, scale-up, and clinical translation, ongoing research efforts offer opportunities for overcoming these obstacles and realizing the potential of SLNs in diabetes management. The potential impact of antidiabetic drug-loaded SLNs in addressing the unmet needs of diabetic patients were substantial. By offering improved drug delivery solutions, SLNs have the potential to revolutionize diabetes therapy by:

Enhancing Treatment Efficacy

SLNs can improve the pharmacokinetics and bioavailability of antidiabetic drugs, leading to better glycemic control and reduced risk of diabetic complications.

Minimizing Side Effects

Targeted delivery of antidiabetic drugs to specific tissues or cells can minimize off-target effects and systemic toxicity, enhancing treatment safety and tolerability.

Improving Patient Adherence

Prolonged drug action and reduced dosing frequency achieved through SLN formulations may improve patient adherence to treatment regimens, leading to better long-term outcomes and quality of life. Overall, antidiabetic drug-loaded SLNs represent a promising approach to address the complex challenges associated with diabetes management, offering hope for improved therapeutic outcomes and enhanced patient care.

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