International Journal of Web of Multidisciplinary Studies
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
website: https://ijwos.com OPEN ACCESS E-ISSN : 3049-2424
Volume 3 Issue 7 , July 2026 DOI: https://doi.org/10.71366/ijwos03072620768

FORMULATION, OPTIMIZATION AND EVALUATION OF SOLID LIPID NANOPARTICLES FOR CO-DELIVERY OF VILDAGLIPTIN AND DAPAGLIFLOZIN IN THE TREATMENT OF TYPE 2 DIABETES MELLITUS

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Article Info

Article History:

Published: 20 July 2026

Publication Issue:
Volume 3, Issue 7
July-2026

Page Number:
391-402

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Abstract:

Type 2 diabetes mellitus (T2DM) is a chronic progressive metabolic disorder characterized by insulin resistance, impaired insulin secretion, excessive hepatic glucose production, dysregulated incretin activity, and altered renal glucose handling. Despite the availability of several pharmacological interventions, achieving sustained glycemic control remains challenging because of disease progression, poor medication adherence, frequent dosing schedules, and long-term complications. Combination therapy targeting multiple pathogenic pathways has therefore emerged as an effective strategy for improving therapeutic outcomes. Among contemporary antidiabetic agents, vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and dapagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, demonstrate complementary mechanisms that collectively improve glycemic control while providing favorable cardiovascular and renal benefits.Conventional oral dosage forms, however, present limitations including pharmacokinetic mismatch, repeated dosing requirements, and variable drug bioavailability. Nanotechnology-based drug delivery systems, particularly solid lipid nanoparticles (SLNs), have gained considerable attention as promising carriers capable of overcoming these limitations. SLNs offer enhanced drug stability, controlled drug release, improved intestinal absorption, protection against enzymatic degradation, and greater patient compliance. Furthermore, the simultaneous encapsulation of hydrophilic and lipophilic antidiabetic drugs within a single lipid matrix provides a novel strategy for synchronized once-daily therapy.

Keywords: Type 2 Diabetes Mellitus; Solid Lipid Nanoparticles; Vildagliptin; Dapagliflozin; DPP-4 Inhibitors; SGLT2 Inhibitors; Nanotechnology; Controlled Drug Delivery; Combination Therapy; Oral Drug Delivery

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic progressive metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance, progressive pancreatic β-cell dysfunction, increased hepatic glucose production, impaired incretin activity, abnormal glucagon secretion, and enhanced renal glucose reabsorption. The disease has become one of the most significant global health challenges because of its rapidly increasing prevalence and its association with serious microvascular and macrovascular complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy.

Although several oral antidiabetic agents are available, long-term glycemic control remains difficult due to the multifactorial nature of T2DM and its progressive course. Monotherapy frequently becomes inadequate over time, making combination therapy an essential strategy for targeting multiple pathogenic pathways simultaneously. Among the newer antidiabetic agents, the combination of vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and dapagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, has attracted considerable attention because of its complementary mechanisms of action. Vildagliptin enhances endogenous incretin activity by inhibiting DPP-4, thereby improving glucose-dependent insulin secretion and suppressing glucagon release. In contrast, dapagliflozin lowers blood glucose independently of insulin by inhibiting renal glucose reabsorption and promoting urinary glucose excretion. Together, these agents provide superior glycemic control while offering additional cardiovascular and renal benefits.

Despite these therapeutic advantages, conventional oral dosage forms have several limitations, including frequent dosing, fluctuations in plasma drug concentrations, reduced bioavailability, and poor patient adherence during long-term treatment. These challenges have encouraged the development of advanced drug delivery systems capable of improving therapeutic efficacy while reducing dosing frequency.

Among various nanotechnology-based drug delivery systems, solid lipid nanoparticles (SLNs) have emerged as promising carriers for oral drug delivery because of their biocompatibility, controlled drug release, improved drug stability, enhanced intestinal absorption, and ability to protect encapsulated drugs from degradation. In addition, SLNs provide opportunities for simultaneous delivery of multiple drugs, making them particularly suitable for combination therapy in chronic diseases such as T2DM.

Co-delivery of vildagliptin and dapagliflozin using SLNs represents an innovative strategy to synchronize drug release, improve pharmacokinetic performance, reduce pill burden, and enhance patient compliance. Furthermore, advances in lipid formulation, optimization techniques, and nanoparticle engineering have expanded the potential of SLNs as an effective platform for oral antidiabetic therapy.

This review summarizes recent advances in SLN-based co-delivery systems for vildagliptin and dapagliflozin, with emphasis on the pathophysiology of T2DM, pharmacological rationale for combination therapy, formulation strategies, characterization methods, recent research developments, and future perspectives for clinical translation.

Type 2 Diabetes Mellitus: Pathophysiology and Therapeutic Challenges

Type 2 diabetes mellitus (T2DM) is a complex and progressive metabolic disorder resulting from multiple pathophysiological abnormalities that collectively impair glucose homeostasis. Unlike Type 1 diabetes mellitus, which is primarily caused by autoimmune destruction of pancreatic β-cells, T2DM develops through a combination of insulin resistance, progressive β-cell dysfunction, excessive hepatic glucose production, impaired incretin response, increased glucagon secretion, enhanced renal glucose reabsorption, and dysregulated lipid metabolism. These abnormalities interact continuously throughout disease progression, making T2DM a multifactorial disorder that requires therapeutic strategies targeting multiple mechanisms rather than a single defect.

One of the earliest pathological events in T2DM is insulin resistance, in which peripheral tissues such as skeletal muscle, adipose tissue, and the liver exhibit reduced responsiveness to insulin. As a result, glucose uptake by muscle decreases while hepatic glucose production remains elevated despite hyperglycemia. Initially, pancreatic β-cells compensate by increasing insulin secretion; however, prolonged metabolic stress eventually leads to β-cell dysfunction and a progressive decline in insulin production. Consequently, fasting and postprandial blood glucose concentrations continue to rise, accelerating disease progression.

A major advancement in understanding T2DM was the introduction of the "Ominous Octet" concept by DeFronzo, which describes the eight principal defects contributing to chronic hyperglycemia. These include decreased insulin secretion by pancreatic β-cells, increased glucagon secretion from α-cells, enhanced hepatic glucose production, reduced peripheral glucose uptake, increased lipolysis, diminished incretin effect, increased renal glucose reabsorption, and neurotransmitter dysfunction within the central nervous system. This concept highlights why monotherapy frequently fails to maintain long-term glycemic control and supports the use of combination therapies capable of simultaneously targeting multiple pathogenic pathways.

In addition to hyperglycemia, T2DM is associated with chronic low-grade inflammation, oxidative stress, endothelial dysfunction, and abnormal lipid metabolism. Persistent elevation of blood glucose promotes the formation of advanced glycation end products (AGEs), activation of inflammatory pathways, and excessive production of reactive oxygen species (ROS). These pathological processes contribute significantly to the development of diabetic nephropathy, retinopathy, neuropathy, cardiovascular disease, and other long-term complications. Therefore, modern diabetes management aims not only to reduce blood glucose levels but also to minimize cardiovascular and renal risks while preserving pancreatic β-cell function.

Current treatment guidelines recommend individualized therapy based on disease severity, patient characteristics, and associated comorbidities. Metformin remains the preferred first-line pharmacological agent because of its proven efficacy, safety, and low cost. However, progressive β-cell failure frequently necessitates the addition of other antidiabetic agents, including DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, sulfonylureas, thiazolidinediones, or insulin therapy. Among these options, the combination of DPP-4 and SGLT2 inhibitors has gained considerable attention because these drug classes exhibit complementary mechanisms of action with a low risk of hypoglycemia and additional cardiovascular and renal benefits.

Despite significant advances in pharmacotherapy, long-term diabetes management continues to face several challenges. Conventional oral formulations often require repeated daily administration, resulting in increased pill burden and poor medication adherence. Furthermore, differences in the pharmacokinetic profiles of individual drugs may reduce therapeutic efficiency when administered separately. These limitations have stimulated growing interest in advanced drug delivery systems capable of providing synchronized drug release, improving oral bioavailability, and reducing dosing frequency.

Nanotechnology-based delivery systems, particularly solid lipid nanoparticles (SLNs), have emerged as promising carriers capable of addressing these challenges. Their ability to encapsulate antidiabetic agents, protect drugs from degradation, improve intestinal absorption, and provide sustained drug release makes them attractive candidates for combination therapy. Co-delivery of vildagliptin and dapagliflozin within a single SLN formulation may improve pharmacokinetic synchronization, reduce pill burden, and enhance patient compliance, thereby offering a more effective therapeutic approach for long-term management of T2DM.

Table 1. Major Pathophysiological Defects in Type 2 Diabetes Mellitus

Defect	Physiological Consequence	Therapeutic Target
β-cell dysfunction	Reduced insulin secretion	DPP-4 inhibitors, GLP-1 receptor agonists
Insulin resistance	Decreased glucose uptake	Metformin, Thiazolidinediones (TZDs)
Increased hepatic glucose production	Elevated fasting glucose	Metformin
Increased glucagon secretion	Excess hepatic glucose output	DPP-4 inhibitors
Reduced incretin effect	Decreased insulin response	DPP-4 inhibitors, GLP-1 receptor agonists
Increased renal glucose reabsorption	Persistent hyperglycemia	SGLT2 inhibitors
Increased lipolysis	Elevated free fatty acids	TZDs
Neurotransmitter dysfunction	Impaired appetite and metabolism	GLP-1 receptor agonists

Vildagliptin and Dapagliflozin Combination Therapy: Pharmacological Rationale

The progressive nature of Type 2 diabetes mellitus (T2DM) necessitates therapeutic strategies that simultaneously target multiple pathophysiological defects. As β-cell function progressively declines and insulin resistance worsens, monotherapy often fails to maintain adequate glycemic control. Consequently, combination therapy has become a cornerstone of modern T2DM management because it improves glycemic control while minimizing adverse effects and delaying disease progression.

Among the available therapeutic combinations, vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and dapagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, have gained considerable attention due to their complementary mechanisms of action. Since these drugs regulate blood glucose through independent physiological pathways, their combination produces additive therapeutic benefits without substantially increasing the risk of hypoglycemia.

Vildagliptin

Vildagliptin is a potent and selective DPP-4 inhibitor that enhances the activity of endogenous incretin hormones, primarily glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Under physiological conditions, these incretin hormones stimulate glucose-dependent insulin secretion while suppressing glucagon release after food intake. However, they are rapidly degraded by the DPP-4 enzyme. By inhibiting DPP-4, vildagliptin prolongs incretin activity, resulting in improved insulin secretion, reduced hepatic glucose production, and better postprandial glucose control.

Unlike insulin secretagogues such as sulfonylureas, vildagliptin stimulates insulin release only when blood glucose levels are elevated, thereby minimizing the risk of hypoglycemia. In addition, it is generally weight neutral and well tolerated, making it suitable for long-term therapy. Nevertheless, its relatively short elimination half-life requires administration twice daily, which may negatively influence patient adherence during chronic treatment.

Dapagliflozin

Dapagliflozin belongs to the SGLT2 inhibitor class and reduces blood glucose through an insulin-independent mechanism. SGLT2 transporters located in the proximal renal tubules normally reabsorb approximately 90% of filtered glucose. Inhibition of these transporters decreases renal glucose reabsorption, leading to increased urinary glucose excretion and a reduction in plasma glucose concentrations.

Beyond glycaemic control, dapagliflozin provides several additional clinical benefits, including modest weight reduction, lowering of blood pressure, and significant cardiovascular and renoprotective effects. Because its glucose-lowering activity is independent of pancreatic β-cell function, dapagliflozin remains effective even in advanced stages of T2DM. Furthermore, its once-daily dosing schedule contributes to improved patient convenience and adherence.

Scientific Basis of Combination Therapy

The combination of vildagliptin and dapagliflozin represents a rational therapeutic approach because each drug targets different components of the pathophysiology of T2DM. Vildagliptin enhances insulin secretion and suppresses glucagon release through incretin-mediated mechanisms, whereas dapagliflozin lowers plasma glucose by promoting urinary glucose excretion independently of insulin. Consequently, simultaneous administration provides complementary glucose-lowering effects without excessive stimulation of insulin secretion.

Several clinical studies have demonstrated that combining DPP-4 inhibitors with SGLT2 inhibitors produces greater reductions in glycated hemoglobin (HbA1c), fasting plasma glucose, and postprandial glucose than either drug alone. Additionally, this therapeutic combination is associated with a low incidence of hypoglycemia, minimal weight gain, and improved cardiovascular and renal outcomes, making it an attractive option for patients requiring long-term diabetes management.

2. Pharmaceutical Challenges

Despite their pharmacological advantages, conventional formulations of vildagliptin and dapagliflozin present several formulation-related challenges. Vildagliptin requires twice-daily administration because of its short biological half-life, whereas dapagliflozin is administered once daily. This mismatch in dosing frequency increases pill burden and may reduce medication adherence, particularly in patients receiving multiple medications for diabetes and associated comorbidities.

In addition, conventional immediate-release formulations produce rapid fluctuations in plasma drug concentrations, resulting in repeated peak and trough levels that may compromise sustained glycemic control. Maintaining synchronized therapeutic concentrations of both drugs using separate formulations remains challenging during long-term treatment.

These limitations highlight the need for innovative drug delivery systems capable of providing synchronized and prolonged release of both drugs from a single dosage form.

Need for SLN-Based Co-delivery

Solid lipid nanoparticles (SLNs) offer an attractive platform for the simultaneous delivery of vildagliptin and dapagliflozin. Their solid lipid matrix protects encapsulated drugs from degradation, improves oral absorption, enables sustained drug release, and enhances formulation stability. Importantly, co-encapsulation of both drugs within a single SLN system may synchronize their pharmacokinetic profiles, potentially extending the release of vildagliptin to better match the once-daily profile of dapagliflozin. Such an approach could reduce dosing frequency, improve patient adherence, decrease pill burden, and enhance overall therapeutic efficacy.

Table 2. Comparison of Vildagliptin and Dapagliflozin

Parameter	**Vildagliptin**	**Dapagliflozin**
Drug Class	DPP-4 inhibitor	SGLT2 inhibitor
Primary Target	DPP-4 enzyme	SGLT2 transporter
Mechanism	Increases GLP-1 and GIP activity	Inhibits renal glucose reabsorption
Insulin Dependence	Glucose-dependent	Insulin-independent
Major Benefit	Improves insulin secretion and suppresses glucagon	Promotes urinary glucose excretion
Dosing Frequency	Twice daily	Once daily
Risk of Hypoglycaemia	Very low	Very low
Additional Benefits	Weight neutral	Weight loss, cardiovascular and renal protection

Solid Lipid Nanoparticles: A Promising Carrier for Combination Drug Delivery

Solid lipid nanoparticles (SLNs) are nanosized colloidal carriers composed of physiologically compatible solid lipids stabilized by surfactants. With particle sizes generally ranging from 50 to 500 nm, SLNs have emerged as an attractive drug delivery system because they combine the advantages of polymeric nanoparticles, liposomes, and emulsions while exhibiting excellent biocompatibility, biodegradability, and physical stability. Their ability to enhance drug solubility, improve oral bioavailability, protect encapsulated drugs from degradation, and provide controlled drug release has made them particularly useful for the delivery of antidiabetic drugs.

SLNs are commonly prepared using lipids such as Compritol® 888 ATO, glyceryl monostearate, stearic acid, and Precirol® ATO 5, together with surfactants including Poloxamer 188, Tween 80, and lecithin. The selection of lipid and surfactant plays a crucial role in determining particle size, drug entrapment efficiency, stability, and drug release behavior.

Various preparation techniques have been employed for SLN production, including hot homogenization, cold homogenization, solvent emulsification–evaporation, microemulsion, and ultrasonication. Among these, hot homogenization followed by probe ultrasonication is the most widely used because it produces nanoparticles with uniform size distribution, high encapsulation efficiency, and good reproducibility.

Drug molecules may be incorporated into SLNs through three principal models: homogeneous matrix, drug-enriched shell, and drug-enriched core. The drug distribution within the lipid matrix directly influences the release pattern and stability of the formulation. Appropriate selection of lipid composition and processing conditions enables sustained drug release while minimizing premature drug leakage.

Compared with conventional oral dosage forms, SLNs offer several advantages, including improved oral bioavailability, controlled and sustained drug release, protection against chemical and enzymatic degradation, reduced dosing frequency, and enhanced patient compliance. In addition, their lipid composition facilitates intestinal lymphatic uptake, which may improve systemic drug absorption.

The co-delivery of vildagliptin and dapagliflozin using SLNs represents a promising strategy for overcoming the limitations of conventional therapy. Encapsulation of both drugs within a single lipid matrix can synchronize their release profiles, improve pharmacokinetic performance, reduce pill burden, and enhance long-term glycaemic control. These characteristics make SLNs a promising platform for the development of advanced oral combination therapies for Type 2 diabetes mellitus.

Advantages of Solid Lipid Nanoparticles in Antidiabetic Drug Delivery

Feature	**Benefit**
Biocompatible lipid matrix	Safe and biodegradable
Controlled drug release	Prolonged therapeutic effect
Improved oral bioavailability	Enhanced drug absorption
Protection of encapsulated drugs	Reduced chemical and enzymatic degradation
High formulation stability	Better shelf life
Co-delivery capability	Simultaneous delivery of multiple drugs
Reduced dosing frequency	Improved patient compliance

Characterization of Solid Lipid Nanoparticles

Physicochemical characterization is essential for evaluating the quality, stability, and performance of solid lipid nanoparticles (SLNs). Parameters such as particle size, polydispersity index (PDI), zeta potential, drug entrapment efficiency, morphology, thermal behavior, and in vitro drug release provide valuable information regarding formulation stability and therapeutic performance.

Particle Size and Polydispersity Index (PDI)

Particle size is one of the most important characteristics affecting drug release, cellular uptake, and oral bioavailability. Smaller nanoparticles possess a larger surface area, leading to improved dissolution and intestinal absorption. Particle size is commonly determined using Dynamic Light Scattering (DLS), while the PDI indicates the uniformity of particle size distribution. A PDI value below 0.3 generally reflects a homogeneous nanoparticle population suitable for pharmaceutical applications.

Zeta Potential

Zeta potential measures the surface charge of nanoparticles and serves as an indicator of colloidal stability. Nanoparticles with sufficiently high positive or negative zeta potential exhibit greater electrostatic repulsion, thereby minimizing particle aggregation during storage. In sterically stabilized SLNs, moderate zeta potential values are generally sufficient to maintain formulation stability.

Drug Entrapment Efficiency and Drug Loading

Entrapment efficiency represents the percentage of drug successfully incorporated within the lipid matrix, whereas drug loading indicates the amount of drug present relative to the total nanoparticle weight. High entrapment efficiency improves sustained drug release and minimizes drug loss during formulation.

Morphological Analysis

The surface morphology and structural characteristics of SLNs are commonly evaluated using Scanning Electron Microscopy (SEM) or Transmission Electron Microscopy (TEM). These techniques provide information regarding particle shape, surface smoothness, aggregation, and particle size. Ideally, SLNs should exhibit a spherical morphology with a uniform size distribution.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis is performed to investigate drug–excipient compatibility and identify possible chemical interactions between the drug and formulation components. The absence of significant changes in characteristic functional group peaks generally indicates compatibility and successful drug incorporation within the lipid matrix.

Differential Scanning Calorimetry (DSC)

DSC is widely employed to study the thermal behavior and crystallinity of lipid nanoparticles. Changes in melting endotherms or disappearance of the drug's characteristic melting peak indicate successful encapsulation and reduced crystallinity, which may contribute to improved drug release and bioavailability.

In Vitro Drug Release

In vitro drug release studies evaluate the release profile of encapsulated drugs under simulated physiological conditions. Release data are further analyzed using kinetic models such as Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models to determine the mechanism of drug release. Sustained and controlled release is generally considered desirable for chronic diseases such as Type 2 diabetes mellitus.

Common Characterization Techniques for Solid Lipid Nanoparticles

Parameter	Analytical Technique	Significance
Particle size	Dynamic Light Scattering (DLS)	Influences bioavailability and drug release
Polydispersity Index	DLS	Indicates particle size uniformity
Zeta potential	Electrophoretic Light Scattering	Predicts colloidal stability
Drug entrapment efficiency	UV-Visible Spectroscopy/HPLC	Determines drug incorporation
Morphology	SEM/TEM	Evaluates particle shape and surface characteristics
Drug–excipient compatibility	FTIR	Detects chemical interactions
Thermal behavior	DSC	Assesses crystallinity and drug encapsulation
Drug release	Dissolution studies	Evaluates release profile and kinetics

Recent Advances in SLN-Based Antidiabetic Drug Delivery

Recent developments in nanotechnology have significantly expanded the application of solid lipid nanoparticles (SLNs) for the treatment of Type 2 diabetes mellitus (T2DM). Owing to their ability to improve drug stability, enhance oral bioavailability, and provide controlled drug release, SLNs have been investigated for the delivery of several antidiabetic agents, including metformin, glibenclamide, sitagliptin, empagliflozin, dapagliflozin, and insulin.

Several studies have demonstrated that SLN formulations improve the pharmacokinetic and pharmacodynamic performance of antidiabetic drugs compared with conventional dosage forms. Enhanced intestinal absorption, prolonged drug release, improved therapeutic efficacy, and reduced dosing frequency have been consistently reported. In addition, lipid nanoparticles protect encapsulated drugs from degradation within the gastrointestinal tract, thereby increasing systemic drug availability.

Recent investigations have also explored dual-drug-loaded SLNs for combination therapy. Co-encapsulation of antidiabetic agents with complementary mechanisms of action has shown improved glycemic control, synchronized drug release, and better patient compliance compared with individual drug administration. These findings support the growing interest in multifunctional lipid-based nanocarriers for diabetes management.

Although several nano formulations containing DPP-4 inhibitors or SGLT2 inhibitors have been reported individually, studies investigating the simultaneous delivery of vildagliptin and dapagliflozin remain limited. Considering their complementary pharmacological actions and favorable clinical outcomes, co-delivery of these agents using SLNs represents a promising strategy for developing a once-daily oral formulation capable of improving therapeutic efficacy while reducing pill burden.

Continued advances in lipid engineering, surface modification, Quality by Design (QbD), and scalable manufacturing technologies are expected to further improve the clinical translation of SLN-based antidiabetic formulations. Future research should focus on optimizing formulation stability, large-scale production, long-term safety evaluation, and clinical validation to facilitate commercialization.

3. Challenges and Future Perspectives

Despite the significant progress achieved in the development of solid lipid nanoparticles (SLNs), several challenges continue to limit their widespread clinical application. One of the major concerns is the limited drug-loading capacity and the possibility of drug expulsion during storage due to lipid crystallization and polymorphic transitions. Maintaining long-term physical stability while preserving high entrapment efficiency remains an important formulation challenge.

Another limitation is the difficulty in achieving consistent large-scale manufacturing without affecting particle size, drug release, and batch-to-batch reproducibility. Moreover, comprehensive studies on long-term safety, regulatory approval, and clinical efficacy are still limited for many SLN-based formulations. These issues must be addressed before successful commercialization.

Future research should focus on the development of optimized lipid compositions, Quality by Design (QbD)-based formulation strategies, and advanced manufacturing technologies to improve formulation robustness and scalability. Surface-functionalized and targeted SLNs may further enhance intestinal absorption, reduce systemic side effects, and improve therapeutic outcomes.

The co-delivery of vildagliptin and dapagliflozin within a single SLN formulation represents a promising approach for next-generation diabetes therapy. Such systems have the potential to provide synchronized drug release, improve patient adherence, reduce dosing frequency, and achieve better long-term glycemic control. Continued preclinical and clinical investigations will be essential to establish the safety, efficacy, and commercial feasibility of these advanced nanocarrier systems.

4. Conclusion

Type 2 diabetes mellitus is a multifactorial metabolic disorder that often requires combination therapy to achieve effective glycemic control and reduce the risk of long-term complications. The combination of vildagliptin and dapagliflozin offers complementary mechanisms of action, resulting in improved glucose regulation with a lower risk of hypoglycemia.

Solid lipid nanoparticles have emerged as a promising oral drug delivery platform because of their ability to enhance drug stability, improve bioavailability, protect drugs from degradation, and provide controlled drug release. Their capability to co-deliver multiple therapeutic agents makes them particularly attractive for combination antidiabetic therapy.

Although challenges related to formulation stability, large-scale manufacturing, and clinical translation remain, ongoing advances in nanotechnology and lipid-based drug delivery are expected to overcome these limitations. Overall, SLN-based co-delivery of vildagliptin and dapagliflozin represents a promising strategy for improving the efficacy, safety, and patient compliance in the management of Type 2 diabetes mellitus, warranting further preclinical and clinical investigation.

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