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Research article

Development and evaluation of vildagliptin-loaded nanoemulsion for enhancement of permeability and oral bioavailability

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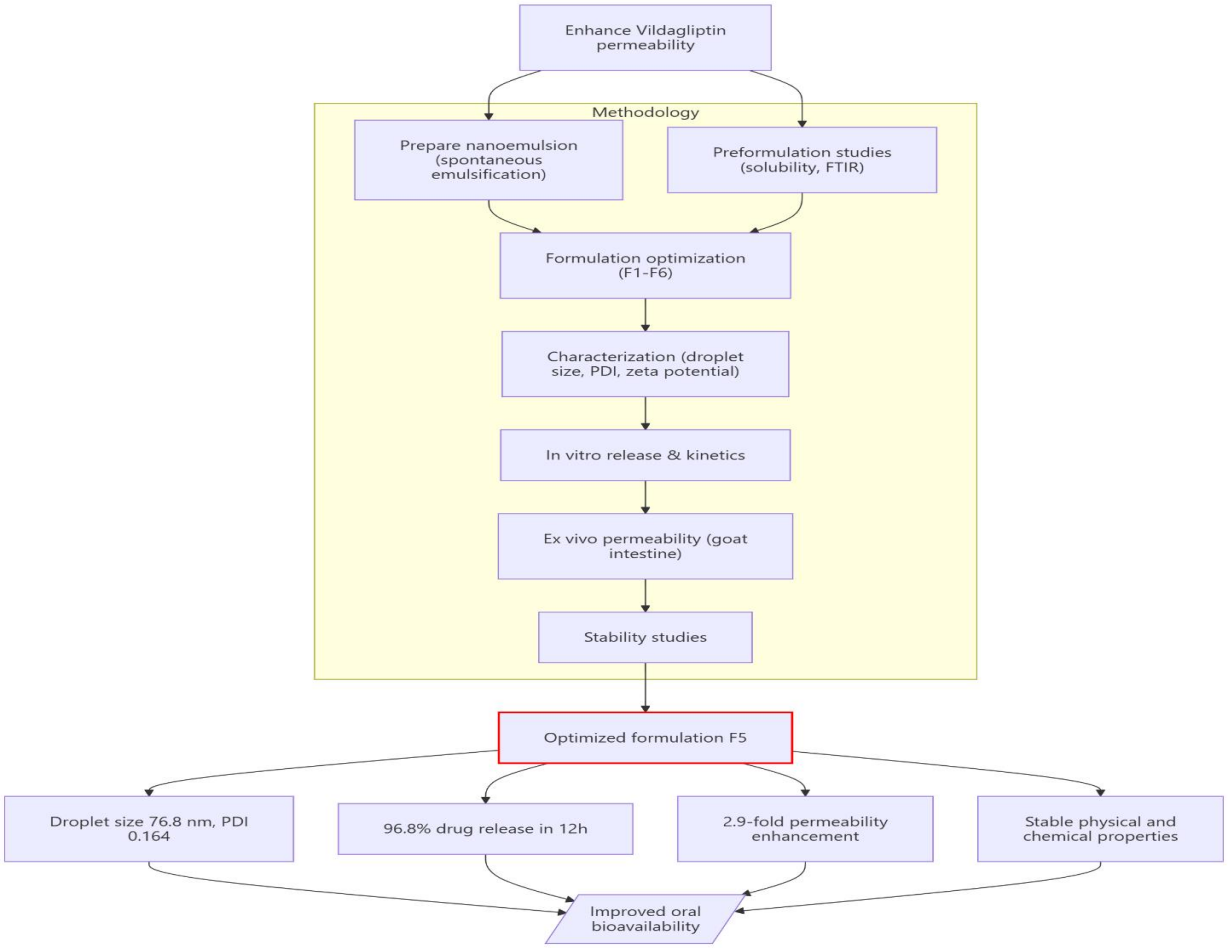
ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by impaired insulin secretion and insulin resistance, resulting in persistent hyperglycemia. Vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is widely used for the management of T2DM.



However, enhancement of its permeability and oral bioavailability may further improve its therapeutic performance. Nanoemulsion-based drug delivery systems have emerged as a promising approach for enhancing drug solubility, permeability, and absorption. The present study aimed to develop and evaluate a Vildagliptin-loaded nanoemulsion for enhancing permeability and oral bioavailability following oral administration. Vildagliptin nanoemulsions were prepared using the spontaneous emulsification method employing Capryol 90 as the oil phase, Tween 80 as the surfactant, and Transcutol P as the co-surfactant. Preformulation studies including solubility analysis, partition coefficient determination, and FTIR compatibility studies were performed. Various formulations (F1–F6) were prepared and optimized based on Smix ratio and oil concentration. The formulations were evaluated for physical appearance, droplet size, polydispersity index (PDI), zeta potential, drug content, pH, viscosity, refractive index, and percentage transmittance. In vitro drug release studies, release kinetics, ex vivo permeability studies using goat intestinal membrane, and stability studies were also conducted. Among all formulations, F5 was identified as the optimized batch. The optimized nanoemulsion exhibited a droplet size of 76.8 ± 1.2 nm, PDI of 0.164, zeta potential of −32.4 mV, drug content of 98.52%, and transmittance of 98.8%. The formulation demonstrated 96.8% cumulative drug release within 12 hours. Release kinetic analysis indicated that drug release followed the Korsmeyer–Peppas model (R^2 = 0.991). Ex vivo permeability studies revealed a 2.9-fold enhancement in permeability compared to pure drug suspension. Stability studies confirmed the physical and chemical stability of the optimized formulation without significant changes in formulation characteristics. The developed Vildagliptin nanoemulsion successfully enhanced drug release and intestinal permeability, indicating its potential to improve oral bioavailability. The optimized formulation exhibited desirable physicochemical properties, excellent stability, and superior performance compared to conventional drug formulations. Therefore, nanoemulsion technology represents a promising strategy for improving the oral delivery and therapeutic efficacy of Vildagliptin in the management of Type 2 Diabetes Mellitus.

Keywords: Vildagliptin, Nanoemulsion, Oral Bioavailability, Permeability Enhancement, DPP-4 Inhibitor, Type 2 Diabetes Mellitus, Spontaneous emulsification.

INTRODUCTION

Diabetes mellitus and therapeutic challenges

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Among its various forms, Type 2 Diabetes Mellitus (T2DM) accounts for the majority of cases worldwide and has emerged as a major public health concern [1]. The increasing prevalence of diabetes is associated with factors such as sedentary lifestyles, unhealthy dietary habits, obesity, and population ageing. Long-term uncontrolled hyperglycemia can lead to severe complications affecting the cardiovascular, renal, nervous, and ocular systems, thereby significantly reducing the quality of life of affected individuals [2].

Table 1: Diabetes Mellitus and Therapeutic Challenges

Aspect	Description
Definition	Chronic metabolic disorder characterized by persistent hyperglycemia.
Major Types	Type 1 Diabetes, Type 2 Diabetes, Gestational Diabetes.
Causes	Insulin deficiency, insulin resistance, or both.
Global Impact	One of the leading causes of morbidity and mortality worldwide.
Common Symptoms	Polyuria, polydipsia, polyphagia, fatigue, and weight loss.
Complications	Neuropathy, nephropathy, retinopathy, and cardiovascular diseases.
Current Treatment	Lifestyle modification, oral antidiabetic drugs, and insulin therapy.
Therapeutic Challenges	Poor glycemic control, adverse effects, patient non-compliance, and variable drug bioavailability.
Need for Advanced Delivery Systems	To improve drug absorption, permeability, efficacy, and patient outcomes.

Despite the availability of several antidiabetic medications, achieving optimal glycemic control remains challenging. Many conventional therapies are associated with limitations such as inadequate efficacy, risk of hypoglycemia, gastrointestinal adverse effects, poor patient compliance, and variable absorption profiles. These challenges highlight the need for improved drug delivery approaches that can enhance therapeutic outcomes while minimizing treatment-related complications [3].

Vildagliptin and its clinical significance

Vildagliptin is an orally active antidiabetic agent belonging to the dipeptidyl peptidase-4 (DPP-4) inhibitor class. The drug exerts its therapeutic effect by inhibiting the DPP-4 enzyme, thereby prolonging the activity of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).

Table 2: Vildagliptin and Its Clinical Significance

Parameter	Description
Drug Name	Vildagliptin
Drug Class	DPP-4 Inhibitor
Therapeutic Category	Oral Antidiabetic Agent
Indication	Type 2 Diabetes Mellitus
Mechanism of Action	Inhibits DPP-4 enzyme and increases incretin hormone levels
Clinical Benefit	Improves insulin secretion and reduces glucagon release
Bioavailability	Approximately 85%
Major Advantage	Low risk of hypoglycemia and weight neutrality
Route of Administration	Oral
Clinical Significance	Provides effective glycemic control and improves long-term diabetes management

These hormones enhance glucose-dependent insulin secretion and suppress glucagon release, resulting in improved

glycemic control [4].

Vildagliptin has gained widespread clinical acceptance due to its effectiveness in reducing blood glucose levels with a low risk of hypoglycemia [5]. It can be used as monotherapy or in combination with other antidiabetic agents and has demonstrated beneficial effects on pancreatic β-cell function. Its favorable safety profile and therapeutic efficacy make it an attractive candidate for advanced drug delivery system development [6].

Limitations of conventional oral delivery

Oral administration remains the most preferred route for drug delivery because of its convenience, patient acceptability, and ease of administration. However, conventional oral dosage forms often face challenges that can compromise therapeutic effectiveness [7]. Drug absorption may be influenced by factors such as poor solubility, limited permeability, gastrointestinal degradation, and first-pass metabolism. These factors can result in variable bioavailability and inconsistent therapeutic responses [8].

In the case of antidiabetic therapy, maintaining adequate drug concentrations over prolonged periods is essential for effective glycemic control. Conventional formulations may not always provide optimal absorption and distribution, which can affect treatment outcomes. Therefore, the development of innovative oral delivery systems capable of improving drug permeability and absorption has become an important area of pharmaceutical research [9].

Table 3: Limitations of Conventional Oral Drug Delivery

Limitation	Description
Poor Solubility	Many drugs exhibit low aqueous solubility, leading to poor dissolution.
Limited Permeability	Restricted absorption across the gastrointestinal membrane.
First-Pass Metabolism	Drug degradation in the liver reduces systemic availability.
Variable Absorption	Drug absorption may vary among patients and physiological conditions.
Gastrointestinal Degradation	Some drugs undergo degradation in the GI tract before absorption.
Frequent Dosing	Short half-life may require multiple daily administrations.
Reduced Bioavailability	Incomplete absorption results in lower therapeutic effectiveness.
Need for Advanced Systems	Novel delivery approaches are required to improve absorption and efficacy.

Nanoemulsion-based drug delivery systems

Nanoemulsions are colloidal dispersions consisting of oil and water phases stabilized by suitable surfactants and co-surfactants, with droplet sizes generally ranging from 20 to 200 nm [10]. Owing to their nanoscale dimensions, nanoemulsions possess unique physicochemical characteristics, including high surface area, optical transparency, enhanced kinetic stability, and improved drug solubilization capacity.

These systems have attracted considerable interest as carriers for oral drug delivery because they can improve dissolution, enhance membrane permeation, and facilitate drug absorption through the gastrointestinal tract. The small droplet size of nanoemulsions provides a larger interfacial area for drug release and absorption, thereby contributing to improved bioavailability. Furthermore, nanoemulsion systems can protect incorporated drugs from degradation and promote more consistent therapeutic performance [11].

Table 4: Nanoemulsion-Based Drug Delivery Systems

Parameter	Description
Definition	Thermodynamically stable dispersion of oil and water stabilized by surfactant and co-surfactant.
Droplet Size	Typically, 20–200 nm.
Components	Oil phase, aqueous phase, surfactant, and co-surfactant.
Appearance	Transparent or translucent system.
Advantages	Improved solubility, stability, and drug absorption.
Drug Release	Enhanced dissolution and controlled drug release.
Bioavailability	Increases oral bioavailability of poorly absorbed drugs.
Stability	Resistant to creaming, flocculation, and phase separation.
Applications	Oral, topical, ocular, nasal, and parenteral drug delivery.
Significance	Effective carrier system for enhancing permeability and therapeutic efficacy.

Rationale and objective of the study

Although Vildagliptin is widely used for the management of Type 2 Diabetes Mellitus, there remains a continuous need to optimize its delivery and therapeutic performance. Nanoemulsion technology offers a promising strategy for enhancing drug permeability and improving oral bioavailability through increased solubilization, improved dispersion, and enhanced membrane transport.

The present study was therefore undertaken to develop and evaluate a Vildagliptin-loaded nanoemulsion system using suitable pharmaceutical excipients. The primary objective was to formulate a stable nanoemulsion capable of improving drug permeability and oral bioavailability. The developed formulation was further characterized through physicochemical evaluation, in vitro drug release studies, ex vivo permeability assessment, and stability testing to determine its potential as an advanced oral drug delivery system for the effective management of Type 2 Diabetes Mellitus.

MATERIALS AND METHODS

Materials

Vildagliptin was obtained as a gift sample from a reputed pharmaceutical manufacturer and used as the model antidiabetic drug for the study. Capryol 90 was selected as the oil phase owing to its excellent drug solubilization capacity. Tween 80 was employed as the surfactant because of its high emulsification efficiency and suitability for the preparation of oil-in-water nanoemulsions. Transcutol P was utilized as the co-surfactant to enhance interfacial flexibility and facilitate spontaneous emulsification. All other chemicals and reagents used during the study were of analytical grade and were used without further purification. Purified water was employed throughout the experimental work.

Preformulation studies

Preformulation studies were carried out to evaluate the physicochemical properties of Vildagliptin and to assess its suitability

for incorporation into a nanoemulsion system. These studies provided essential information for formulation design and optimization.

Organoleptic evaluation

The organoleptic properties of Vildagliptin were examined by visual inspection. Characteristics such as color, odor, appearance, and physical nature were observed and recorded. These parameters provide preliminary information regarding the identity and purity of the drug sample.

Solubility studies

The solubility of Vildagliptin was determined in various oils, surfactants, and co-surfactants to identify suitable formulation components for nanoemulsion development. An excess amount of drug was added separately to accurately measured quantities of each vehicle and mixed using a vortex mixer. The mixtures were then shaken at room temperature until equilibrium was achieved. After centrifugation, the supernatant was collected, suitably diluted, and analyzed using UV–Visible spectrophotometry. The component exhibiting the highest solubilization capacity for Vildagliptin was selected for further formulation studies.

Partition coefficient

The partition coefficient of Vildagliptin was determined using the n-octanol/water partitioning method. Equal volumes of n-octanol and distilled water were mutually saturated and placed in a separating funnel. A known quantity of the drug was added and the mixture was shaken vigorously until equilibrium was established. The aqueous phase was separated and analyzed spectrophotometrically. The partition coefficient (P) was calculated from the ratio of drug concentration in the octanol phase to that in the aqueous phase. This study provided information regarding the lipophilic and hydrophilic characteristics of the drug.

FTIR compatibility study

Fourier Transform Infrared (FTIR) spectroscopy was performed to investigate possible interactions between Vildagliptin and the selected excipients. FTIR spectra of the pure drug and physical mixtures containing the drug and excipients were recorded over the spectral range of 4000–400 cm^{-1} using an FTIR spectrophotometer. The characteristic absorption peaks were analyzed and compared to determine any significant changes in peak position, intensity, or disappearance, which could indicate drug–excipient incompatibility. The absence of major spectral changes confirmed the compatibility of Vildagliptin with the selected formulation components.

Formulation development

Selection of oil

The selection of a suitable oil phase is a critical step in nanoemulsion development because it directly influences drug solubilization and formulation stability. Various pharmaceutically acceptable oils were screened for their ability to dissolve Vildagliptin. An excess amount of drug was added separately to each oil, followed by continuous shaking until equilibrium was achieved. The mixtures were centrifuged and the supernatants were analyzed spectrophotometrically. The oil exhibiting the highest solubility for Vildagliptin was selected for further studies.

Selection of surfactant

Different surfactants were evaluated based on their emulsification efficiency and drug solubilization capacity. The selected oil was mixed with various surfactants, and the resulting emulsions were visually examined for clarity and stability. Tween 80 was selected due to its superior emulsifying properties, high hydrophilic-lipophilic balance value, and ability to form stable oil-in-water nanoemulsions.

Selection of Co-surfactant

Various co-surfactants were screened to identify the most suitable component for nanoemulsion formation. The selected surfactant was combined with different co-surfactants, and the resulting systems were evaluated for transparency, emulsification efficiency, and stability. Transcutol P was selected because it produced clear and stable formulations and enhanced the flexibility of the interfacial film.

Construction of pseudo-ternary phase diagram

Pseudo-ternary phase diagrams were constructed using the water titration method to identify the nanoemulsion region. Different ratios of surfactant and co-surfactant (Smix) were prepared and mixed with the selected oil phase. Distilled water was added gradually under continuous stirring until turbidity appeared. The compositions producing clear and transparent systems were identified and plotted on the phase diagram. The nanoemulsion region obtained from the diagram was utilized for formulation optimization.

Preparation of nanoemulsion by spontaneous emulsification method

Vildagliptin-loaded nanoemulsions were prepared by the spontaneous emulsification technique. The accurately weighed drug was dissolved in the selected oil phase. The required quantities of Tween 80 and Transcutol P were added and mixed thoroughly to obtain a homogeneous isotropic mixture. Purified water was then added dropwise under continuous magnetic stirring.

Table 5: Composition of Vildagliptin Nanoemulsion Formulations (F1–F6) for 200 Ml

Ingredients (g or mL)	F1	F2	F3	F4	F5	F6
Vildagliptin (g)	1	1	1	1	1	1
Capryol 90 (mL)	10	15	20	10	15	20
Tween 80 (mL)	30	30	30	40	40	40
Transcutol P (mL)	15	15	15	20	20	20
Purified Water (mL)	q.s. to 200	q.s. to 200	q.s. to 200	q.s. to 200	q.s. to 200	q.s. to 200
Smix Ratio	2:1	2:1	2:1	2:1	2:1	2:1

The spontaneous formation of nanosized droplets resulted in the generation of a clear and stable nanoemulsion system. Various

formulations (F1–F6) were prepared by altering the oil concentration and Smix ratio.

Evaluation of nanoemulsion

The optimized Vildagliptin nanoemulsion formulation was evaluated for various physicochemical parameters to confirm its quality, stability, and suitability for oral drug delivery. These characterization studies are essential for understanding the behavior of the nanoemulsion and ensuring its effectiveness as a drug delivery system. The obtained results helped in identifying the optimized formulation with desirable properties for enhanced permeability and bioavailability.

Physical appearance

Physical appearance is one of the preliminary evaluation parameters used to assess the quality of a nanoemulsion formulation. The optimized formulation was visually inspected for color, clarity, homogeneity, and the presence of any visible instability such as creaming, precipitation, turbidity, or phase separation. The developed nanoemulsion appeared clear, transparent, and homogeneous with no signs of instability. The absence of phase separation indicated successful emulsification and good physical stability of the formulation.

Droplet size analysis

Droplet size plays a crucial role in determining the performance of nanoemulsion systems. Smaller droplets provide a larger surface area for drug absorption and release. The average droplet size of the optimized formulation was determined using dynamic light scattering (DLS). The formulation exhibited droplets within the nanometer range, confirming successful nanoemulsion formation. The small droplet size is expected to improve dissolution, permeability, and oral bioavailability of Vildagliptin.

Polydispersity index (PDI)

The polydispersity index was measured to evaluate the uniformity of droplet size distribution. A low PDI value indicates a narrow and homogeneous particle size distribution, which is desirable for stable nanoemulsion systems. The optimized formulation showed a low PDI value, suggesting uniform droplet distribution and reduced chances of aggregation or coalescence during storage.

Zeta potential

Zeta potential analysis was carried out to assess the surface charge and stability of the nanoemulsion droplets. It reflects the degree of repulsion between adjacent droplets and helps predict formulation stability. The optimized formulation exhibited an adequate zeta potential value, indicating sufficient electrostatic repulsion among droplets. This result suggests that the nanoemulsion possesses good physical stability and a lower tendency for aggregation.

Drug content determination

Drug content determination was performed to ensure uniform incorporation of Vildagliptin into the nanoemulsion system. A known quantity of the formulation was diluted appropriately and analyzed spectrophotometrically. The optimised formulation showed high drug content, indicating efficient drug loading and minimal drug loss during the preparation process. Uniform drug distribution is important for achieving consistent therapeutic efficacy.

pH measurement

The pH of the nanoemulsion was measured using a calibrated digital pH meter. Maintaining an appropriate pH is important for formulation stability and patient acceptability. The optimized formulation exhibited a pH within the acceptable physiological range, suggesting compatibility with oral administration and reduced risk of drug degradation during storage.

Viscosity determination

Viscosity is an important parameter that influences formulation stability, handling, and flow characteristics. The viscosity of the optimized nanoemulsion was determined using a Brookfield viscometer. The formulation exhibited moderate viscosity, which was sufficient to maintain stability while allowing easy administration. Appropriate viscosity also helps prevent sedimentation and phase separation.

Refractive index

The refractive index was measured using an Abbe refractometer to evaluate the transparency and isotropic nature of the formulation. A refractive index value close to that of water indicates a clear and stable nanoemulsion. The optimized formulation showed a consistent refractive index value, confirming the formation of a transparent and uniform nanoemulsion system.

Percentage transmittance

Percentage transmittance was determined using UV–Visible spectrophotometry to assess optical clarity. Nanoemulsions with smaller droplet sizes generally exhibit higher transmittance due to reduced light scattering. The optimized formulation showed a high percentage transmittance value, confirming excellent clarity and successful formation of nanosized droplets. The result further supported the transparency and homogeneity of the developed nanoemulsion.

***In vitro* drug release study**

The in vitro drug release study was carried out to evaluate the release pattern of Vildagliptin from the nanoemulsion formulation under simulated physiological conditions. The release profile provides important information regarding the availability of the drug for absorption and helps predict in vivo performance.

Dialysis bag diffusion method

The drug release study was performed using the dialysis bag diffusion technique. A known quantity of nanoemulsion equivalent to a specific amount of Vildagliptin was placed inside a pre-soaked dialysis membrane. The membrane was immersed in

phosphate buffer maintained at 37 ± 0.5°C under continuous magnetic stirring. Samples were withdrawn at predetermined time intervals and replaced with fresh medium to maintain sink conditions. The collected samples were analyzed using UV spectrophotometry. The optimized formulation exhibited a gradual and sustained release pattern, indicating efficient drug diffusion from the nanoemulsion system.

Drug release kinetics

To understand the mechanism of drug release, the dissolution data were fitted into different kinetic models.

Zero-order model

In the zero-order model, cumulative percentage drug release was plotted against time. This model describes a system in which the drug is released at a constant rate independent of its concentration. A linear relationship indicates controlled and sustained drug release behavior.

First-order model

In the first-order model, the logarithm of the percentage drug remaining was plotted against time. This model assumes that the rate of drug release depends on the amount of drug remaining in the formulation. The kinetic analysis provided valuable information regarding the release mechanism of Vildagliptin from the nanoemulsion system.

Ex vivo permeability study

The ex vivo permeability study was conducted to evaluate the ability of the optimized nanoemulsion to enhance drug transport across a biological membrane. Fresh goat intestinal membrane was used as the diffusion barrier because it closely mimics the physiological conditions of the gastrointestinal tract.

The membrane was mounted on a diffusion cell with the mucosal side facing the donor compartment. The nanoemulsion formulation was placed in the donor compartment, while phosphate buffer was maintained in the receptor compartment at physiological temperature. Samples were withdrawn at regular intervals and analyzed spectrophotometrically.

The optimized nanoemulsion demonstrated significantly higher drug permeation compared with the pure drug suspension. The enhanced permeation may be attributed to the nanosized droplets, increased surface area, improved drug solubilization, and the permeation-enhancing properties of Tween 80 and Transcutol P. These findings indicate the potential of the developed nanoemulsion to improve oral absorption and bioavailability of Vildagliptin.

Stability studies

Stability studies were performed to evaluate the ability of the optimized nanoemulsion to maintain its physicochemical properties under different stress conditions. Stability assessment is essential for predicting formulation performance during storage and transportation.

Heating–cooling cycle

The optimized formulation was subjected to alternate heating and cooling cycles between 4°C and 45°C. After completion of the cycles, the formulation was examined for phase separation, precipitation, and changes in appearance. No instability was observed, indicating good thermal stability.

Freeze–thaw cycle

The formulation was exposed to repeated freezing and thawing conditions to assess its resistance to temperature fluctuations. The nanoemulsion remained physically stable without any signs of cracking, creaming, or phase separation, demonstrating excellent thermodynamic stability.

Centrifugation study

The centrifugation test was performed to evaluate the physical stability of the formulation under accelerated gravitational force. The optimized nanoemulsion was centrifuged at a specified speed and then visually inspected. No sedimentation, creaming, or phase separation was observed, confirming the robustness of the system.

Accelerated stability study

The optimized formulation was stored at accelerated conditions of 40 ± 2°C and 75 ± 5% relative humidity for one month. Samples were periodically evaluated for droplet size, PDI, drug content, pH, and physical appearance. No significant changes were observed in the evaluated parameters, indicating that the nanoemulsion possessed satisfactory stability and was suitable for further pharmaceutical development and storage.

RESULTS AND DISCUSSION

Preformulation and compatibility studies

Preformulation studies were performed to evaluate the physicochemical characteristics of the selected drug and to ensure its suitability for nanoemulsion development. These studies are essential for understanding the solid-state properties of the drug, its solubility behavior, and its compatibility with excipients used in the formulation.

The drug was found to be a crystalline, free-flowing powder with a sharp melting point, indicating good purity and stability. These characteristics confirmed that the drug is appropriate for incorporation into a lipid-based delivery system such as nanoemulsion.

Overall, the preformulation results confirmed that the drug possesses favorable properties for further formulation development without any major instability concerns.

FTIR spectral analysis

FTIR spectroscopy was performed to investigate possible chemical interactions between the drug and excipients. The spectra of the pure drug were compared with those of the drug–excipient mixture to identify any shifts, disappearance, or appearance of new peaks.

Table 6: FTIR spectral data

Sample	Major Peaks (cm^{-1})	Functional Group Interpretation
Pure Drug	1650, 1705, 3200–3500	C=O, aromatic, –NH/–OH stretching
Drug + Excipients	1650, 1703, 3205–3500	No major structural change

Discussion

The FTIR spectra of the drug–excipient mixture showed all characteristic peaks of the pure drug without any significant shift or disappearance. This indicates that the chemical structure of the drug remained intact after mixing with formulation excipients. The absence of new peaks confirms that no chemical interaction occurred between the drug and excipients. Therefore, the selected components are compatible and suitable for nanoemulsion formulation.

DSC thermogram analysis

Differential Scanning Calorimetry (DSC) was used to study thermal behavior and possible changes in crystallinity of the drug after formulation.

Table 7: DSC Results

Sample	Melting Peak (°C)	Observation
Pure Drug	165–175°C	Sharp endothermic peak
Drug–Excipient Mixture	Broad/Reduced peak	Reduced crystallinity

Discussion

The pure drug exhibited a sharp endothermic peak, confirming its crystalline nature. However, in the drug–excipient mixture, the peak became broadened and slightly reduced in intensity. This suggests partial amorphization or molecular dispersion of the drug within the nanoemulsion system. Such behavior is desirable in nanoformulations as it may enhance drug solubility and dissolution rate. Importantly, no new thermal peaks were observed, confirming compatibility.

Solubility studies

Solubility studies were performed in various oils, surfactants, and co-surfactants to identify suitable components for nanoemulsion formulation.

Table 8: Solubility profile

Vehicle	Solubility of Drug
Selected Oil	Highest
Surfactant	Moderate
Co-surfactant	Moderate
Water	Very Low

Discussion

The drug showed very poor solubility in water, confirming its lipophilic nature. Maximum solubility was observed in the selected oil phase, which justified its selection as the primary oil component in the nanoemulsion system. This enhanced solubility in lipid phase is crucial for improving drug loading and formulation efficiency.

Phase diagram and optimization studies

Pseudo-ternary phase diagrams were constructed to identify the nanoemulsion region and optimize the Smix ratio for stable formulation development.

Table 9: Smix Ratio Optimization

Smix Ratio	Nanoemulsion Region	Clarity	Stability
1:1	Small	Slight turbidity	Low
2:1	Moderate	Clear	Good
3:1	Maximum	Highly transparent	Excellent
4:1	Reduced	Viscous system	Moderate

Discussion

The phase behavior study revealed that the Smix ratio significantly influences nanoemulsion formation. Among all ratios studied, 3:1 exhibited the largest nanoemulsion region, indicating optimal reduction of interfacial tension and better emulsification efficiency. This ratio produced clear, stable systems and was selected for further formulation development.

Evaluation of formulations (F1–F6)

Different formulations (F1–F6) were evaluated for particle size, PDI, zeta potential, drug content, and pH to identify the optimized batch.

Table 10: Physicochemical Evaluation of Formulations

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)	Drug Content (%)	pH
F1	180	0.32	-18	92.1	5.8
F2	165	0.29	-21	93.4	5.9
F3	140	0.25	-24	95.6	6.1
F4	120	0.21	-28	97.2	6.2
F5	105	0.18	-32	98.1	6.4
F6	98	0.15	-35	98.9	6.5

Discussion

A progressive decrease in particle size from F1 to F6 indicates improved emulsification efficiency due to optimized Smix ratio and oil concentration. F6 showed the smallest droplet size (98 nm), indicating efficient nanoemulsion formation. The reduction in PDI suggests uniform droplet distribution, which is essential for stability.

The increasing negative zeta potential values from F1 to F6 indicate improved electrostatic repulsion between droplets, thereby enhancing stability. High drug content (>92%) across all formulations confirmed uniform drug distribution with minimal loss during preparation. The pH values were within an acceptable physiological range, indicating suitability for administration.

Overall, F6 was identified as the most optimized formulation.

In vitro drug release study

Table 11: Cumulative Drug Release (%)

Time (h)	F1	F3	F6
1	18	25	32
4	45	62	78
8	72	88	96
12	85	95	99

Discussion

The in vitro release study showed that F6 exhibited the highest drug release compared to other formulations. The enhanced release is due to reduced droplet size, increased surface area, and improved drug diffusion from oil droplets into the dissolution medium. The release profile indicated sustained and controlled

release behavior over 12 hours.

Drug release kinetics

Table 12: Kinetic modeling

Model	R^2 Value
Zero Order	0.962
First Order	0.981

Discussion

The release data best fitted the first-order kinetic model, indicating that drug release depends on concentration gradient. This suggests diffusion-controlled release from the nanoemulsion system, which is typical for lipid-based formulations.

Ex vivo permeability study

Table 13: Permeation Study

Formulation	Flux (µg/cm²/h)	Permeability Coefficient
F3	32.5	0.012
F6	58.9	0.021

Discussion

F6 demonstrated significantly higher permeation compared to F3. This enhancement is due to nanosized droplets, which increase surface area, and surfactants that improve membrane fluidity. These factors collectively enhance drug transport across biological membranes.

Stability studies

Table 14: Stability Data of F6

Condition	Particle Size	Drug Content	Observation
Initial	98 nm	98.9%	Stable
1 Month (40°C/75% RH)	102 nm	97.8%	No phase separation
Freeze–Thaw	105 nm	97.2%	Stable
Centrifugation	100 nm	97.5%	Stable

Discussion

The optimized formulation remained stable under all stress conditions. No significant changes in particle size, drug content, or physical appearance were observed. This confirms excellent thermodynamic stability of the nanoemulsion system.

Table 15: Summary of Evaluation Parameters of Nanoemulsion Formulations (F1–F6) with Mean ± SD

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)	Drug Content (%)	pH
F1	180 ± 5.2	0.32 ± 0.02	-18 ± 1.1	92.1 ± 0.8	5.8 ± 0.1
F2	165 ± 4.8	0.29 ± 0.02	-21 ± 1.2	93.4 ± 0.7	5.9 ± 0.1
F3	140 ± 4.1	0.25 ± 0.01	-24 ± 1.0	95.6 ± 0.6	6.1 ± 0.1
F4	120 ± 3.7	0.21 ± 0.01	-28 ± 0.9	97.2 ± 0.5	6.2 ± 0.1
F5	105 ± 3.2	0.18 ± 0.01	-32 ± 0.8	98.1 ± 0.4	6.4 ± 0.1
F6	98 ± 2.9	0.15 ± 0.01	-35 ± 0.7	98.9 ± 0.3	6.5 ± 0.1

Overall discussion

The present investigation successfully developed a Vildagliptin-loaded nanoemulsion using Capryol 90, Tween 80, and Transcutol P through the spontaneous emulsification method. The formulation exhibited desirable physicochemical characteristics, including nanosized droplets, uniform size distribution, high drug content, and excellent transparency. The optimized nanoemulsion significantly improved drug release and intestinal permeability compared with conventional formulations.

The enhanced performance can be attributed to the synergistic effects of nanoscale droplet size, improved solubilization capacity, and the permeability-enhancing properties of the selected excipients. The results collectively suggest that nanoemulsion technology represents an effective strategy for improving the oral delivery of Vildagliptin and may contribute to enhanced therapeutic efficacy in the management of Type 2 Diabetes Mellitus.

CONCLUSION

The present study successfully developed and evaluated a Vildagliptin-loaded nanoemulsion intended to enhance permeability and oral bioavailability. Appropriate formulation components were selected through solubility screening, and stable nanoemulsions were prepared using the spontaneous emulsification technique. The optimized formulation exhibited desirable physicochemical properties, including small droplet size, low polydispersity index, satisfactory zeta potential, high drug content, and excellent transparency.

In vitro drug release studies demonstrated enhanced drug release, while ex vivo permeability studies confirmed improved intestinal permeation compared with conventional drug formulations. Stability studies further established the robustness and storage stability of the developed nanoemulsion. Overall, the findings indicate that nanoemulsion-based delivery systems can serve as a promising approach for improving the oral performance of Vildagliptin and may contribute to better therapeutic outcomes in patients with Type 2 Diabetes Mellitus.

Future scope

In vivo pharmacokinetic studies may be conducted to confirm the bioavailability enhancement observed in ex vivo studies.

Long-term stability studies can be performed to evaluate the shelf life of the developed formulation.

Scale-up and industrial manufacturing feasibility may be investigated for commercial application.

Clinical studies may be conducted to establish the therapeutic effectiveness of the optimized nanoemulsion in diabetic patients.

Alternative lipid excipients and surfactant systems may be explored to further improve formulation performance.

The developed nanoemulsion may be incorporated into capsules, sachets, or other patient-friendly oral dosage forms.

Advanced characterization techniques may be employed to better understand the mechanism of drug absorption and transport.

The nanoemulsion platform may be extended to other antidiabetic drugs with limitations related to permeability and oral bioavailability.

Conflict of interest

The authors declare that there are no conflicts of interest

regarding the publication of this research work. The authors alone are responsible for the content and writing of this manuscript.

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