EJPMR, 2026, 13(7), 590-596 **Research Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

OPTIMIZATION OF TRANSDERMAL NANOPARTICLES FOR INSULIN DELIVERY

Sohan Lal Gurjar[1]*, Prof. Dr. Pankaj Kumar Sharma[2], Prof. Dr. Jaya Sharma[3], Prof. Dr. Rekha Kanwar[4], Dr. Monika Jain[5]

[1]Research Scholar, Apex Institute of Pharmaceutical Sciences, Apex University, Jaipur, Rajasthan, India.
[2]Dean, Apex Institute of Pharmaceutical Sciences, Apex University, Jaipur, Rajasthan, India.
[3]Principal, Apex Institute of Pharmaceutical Sciences, Apex University, Jaipur, Rajasthan, India.
[4]Associate Professor, Apex Institute of Pharmaceutical Sciences, Apex University, Jaipur, Rajasthan, India.
[5]Professor, Apex Institute of Pharmaceutical Sciences, Apex University, Jaipur, Rajasthan, India.

***Corresponding Author: Sohan Lal Gurjar**

Research Scholar, Apex Institute of Pharmaceutical Sciences, Apex University, Jaipur, Rajasthan, India.

DOI: https://doi.org/10.5281/zenodo.21353657

How to cite this Article: Sohan Lal Gurjar[1]*, Prof. Dr. Pankaj Kumar Sharma[2], Prof. Dr. Jaya Sharma[3], Prof. Dr. Rekha Kanwar[4], Dr. Monika Jain[5] (2026). Optimization Of Transdermal Nanoparticles For Insulin Delivery. European Journal of Pharmaceutical and Medical Research, 13(7), 590–596.

Article Received on 21/05/2026 **Article Revised on 11/06/2026** **Article Published on 01/07/2026**

ABSTRACT

Diabetes mellitus is one of the most prevalent chronic metabolic disorders worldwide and is characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. Despite significant advancements in diabetes management, the conventional subcutaneous administration of insulin remains associated with several limitations, including pain, poor patient compliance, risk of infection, local tissue irritation, and fluctuating plasma insulin levels. These challenges have prompted extensive research into alternative, patient-friendly drug delivery systems. Among these, transdermal drug delivery has emerged as a promising non-invasive approach due to its ability to provide sustained drug release, improve patient adherence, and reduce systemic side effects. However, the large molecular size, hydrophilic nature, and enzymatic instability of insulin significantly restrict its permeation through the stratum corneum, the primary barrier of the skin. Nanoparticle-based delivery systems have demonstrated considerable potential in overcoming these physiological barriers by enhancing drug stability, facilitating skin penetration, and enabling controlled insulin release. The present study focuses on the optimization of transdermal nanoparticles for insulin delivery with the objective of developing a stable, efficient, and biocompatible carrier system capable of improving insulin permeation across the skin. Polymeric or lipid-based nanoparticles are formulated using suitable preparation techniques, and critical formulation variables such as polymer concentration, surfactant concentration, drug-to-polymer ratio, and process parameters are systematically optimized to achieve desirable physicochemical characteristics. The prepared nanoparticles are evaluated for particle size, polydispersity index, zeta potential, drug loading capacity, encapsulation efficiency, morphology, in vitro drug release, and stability. Furthermore, the optimized nanoparticle formulation is incorporated into a transdermal delivery system and assessed for skin permeation, drug retention, biocompatibility, and pharmacodynamic performance using suitable in vitro and ex vivo models. Optimization through statistical design approaches ensures the identification of the most influential formulation variables while minimizing experimental variability. The optimized transdermal nanoparticle formulation is expected to exhibit high encapsulation efficiency, nanoscale particle size, sustained insulin release, enhanced skin permeation, and improved physicochemical stability without compromising the biological activity of insulin. Such a delivery system may effectively maintain therapeutic plasma insulin concentrations for prolonged periods while minimizing the frequency of administration and improving patient comfort. Additionally, the incorporation of nanoparticles into transdermal systems may protect insulin from enzymatic degradation and facilitate controlled release, thereby enhancing therapeutic efficacy. In conclusion, the optimization of transdermal nanoparticles represents a promising strategy for the non-invasive delivery of insulin and has the potential to overcome the limitations associated with conventional insulin therapy.

The successful development of an optimized nanoparticle-based transdermal formulation may contribute significantly to improving glycemic control, enhancing patient compliance, reducing treatment-associated complications, and advancing the field of nanotechnology-based drug delivery systems for diabetes management.

KEYWORDS: Diabetes mellitus, insulin delivery, transdermal drug delivery, nanoparticles, formulation optimization, controlled drug release, and skin permeation.

INTRODUCTION

Diabetes mellitus is one of the most prevalent chronic metabolic disorders worldwide and is characterized by persistent hyperglycemia resulting from inadequate insulin secretion, impaired insulin action, or both. According to recent global estimates, the number of individuals living with diabetes continues to rise, posing a significant public health burden. Insulin remains the primary therapeutic agent for the management of Type 1 diabetes mellitus and is also widely used in advanced Type 2 diabetes mellitus. Despite its clinical effectiveness, insulin therapy is predominantly administered through subcutaneous injections, which are associated with several limitations such as pain, needle phobia, poor patient compliance, risk of infection, local tissue irritation, and fluctuating plasma insulin concentrations. These drawbacks have prompted researchers to explore alternative, non-invasive drug delivery systems capable of improving therapeutic outcomes and patient adherence.

Transdermal drug delivery has emerged as an attractive alternative route for systemic administration of therapeutic agents due to its ability to provide sustained and controlled drug release while bypassing the gastrointestinal tract and hepatic first-pass metabolism. This route offers several advantages, including improved patient compliance, reduced dosing frequency, ease of administration, and the possibility of terminating therapy simply by removing the delivery system. However, successful transdermal delivery of insulin remains challenging because insulin is a large hydrophilic peptide molecule with a molecular weight of approximately 5.8 kDa. The highly organized lipid structure of the stratum corneum, the outermost layer of the skin, acts as an effective barrier that significantly restricts the permeation of such macromolecules.

Recent advancements in nanotechnology have revolutionized the field of transdermal drug delivery by introducing nanoparticle-based carrier systems capable of overcoming the skin barrier. Nanoparticles, including polymeric nanoparticles, lipid nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and nanoemulsions, possess unique physicochemical properties such as small particle size, high surface area, enhanced stability, and controlled drug release characteristics. These properties enable nanoparticles to improve drug permeation through the skin by enhancing drug solubility, protecting insulin from enzymatic degradation, and facilitating penetration via hair follicles and intercellular pathways. Furthermore, nanoparticles can be engineered with surface modifications and biocompatible polymers to enhance skin adhesion, prolong residence time, and achieve targeted delivery.

Optimization of transdermal nanoparticle formulations is a critical step in developing an efficient insulin delivery system. Various formulation parameters, including particle size, zeta potential, encapsulation efficiency, polymer-to-drug ratio, lipid composition, surfactant concentration, and preparation techniques, significantly influence the therapeutic performance of nanoparticles. Statistical tools such as Design of Experiments (DoE) and Response Surface Methodology (RSM) are increasingly employed to optimize these variables systematically, ensuring maximum drug loading, controlled release, enhanced permeation, and formulation stability. The optimized formulation must also exhibit desirable physicochemical characteristics, biocompatibility, and reproducibility for successful clinical translation.

Several studies have demonstrated that nanoparticle-mediated transdermal insulin delivery can achieve prolonged hypoglycemic effects, improved bioavailability, and reduced dosing frequency compared with conventional insulin injections. The incorporation of permeation enhancers, microneedles, iontophoresis, sonophoresis, or chemical enhancers alongside nanoparticle systems has further enhanced transdermal transport of insulin, opening new possibilities for non-invasive diabetes management. Such innovative approaches have the potential to reduce patient discomfort and improve long-term treatment adherence.

Therefore, the optimization of transdermal nanoparticles for insulin delivery represents a promising and rapidly evolving area of pharmaceutical research. By integrating nanotechnology with advanced formulation strategies, researchers aim to develop a safe, effective, and patient-friendly insulin delivery system capable of overcoming the limitations of injectable therapy. The successful development of optimized transdermal nanoparticle formulations may significantly improve glycemic control, enhance quality of life for diabetic patients, and contribute to the advancement of next-generation drug delivery technologies.

MATERIALS AND METHODS

Study Design

The present study was designed to formulate, optimize, and evaluate insulin-loaded polymeric nanoparticles for transdermal drug delivery. A systematic Quality by Design (QbD) approach was adopted to optimize the formulation variables affecting nanoparticle

characteristics and transdermal permeation. The optimized nanoparticles were incorporated into a transdermal gel and evaluated for their physicochemical properties, in vitro drug release, ex vivo skin permeation, and stability.

Materials

Human recombinant insulin was selected as the model antidiabetic drug. Chitosan was used as the biodegradable polymer due to its biocompatibility and mucoadhesive properties. Sodium tripolyphosphate (TPP) served as the cross-linking agent for nanoparticle formation. Polyvinyl alcohol (PVA) and Tween 80 were used as stabilizers and surfactants, respectively. Carbopol 934 was employed as the gel-forming polymer, while propylene glycol was incorporated as a permeation enhancer. Glycerin was used as a humectant, and triethanolamine was added for pH adjustment. Phosphate buffer saline (PBS, pH 7.4) was used as the dissolution medium. Hydrochloric acid, sodium hydroxide, acetic acid, and distilled water were used wherever required. All chemicals and reagents used in the study were of analytical grade.

Instruments

The study utilized a magnetic stirrer, probe sonicator, high-speed homogenizer, dynamic light scattering (DLS) particle size analyzer, zeta potential analyzer, UV–Visible spectrophotometer, Fourier Transform Infrared (FTIR) spectrophotometer, Differential Scanning Calorimeter (DSC), Scanning Electron Microscope (SEM), Transmission Electron Microscope (TEM), Franz diffusion cell assembly, Brookfield viscometer, digital pH meter, analytical balance, centrifuge, freeze dryer (lyophilizer), and a stability chamber maintained according to ICH guidelines.

Preparation of Insulin-Loaded Nanoparticles

Insulin-loaded chitosan nanoparticles were prepared by the ionic gelation method. Chitosan was dissolved in 1% (v/v) acetic acid solution under continuous magnetic stirring until a clear polymeric solution was obtained. Human recombinant insulin was dissolved separately in phosphate buffer (pH 7.4). Sodium tripolyphosphate (TPP) was dissolved in distilled water to prepare the cross-linking solution.

The insulin solution was slowly added to the chitosan solution with continuous stirring. Subsequently, the TPP solution was added dropwise under constant stirring at 1000 rpm. The electrostatic interaction between the positively charged amino groups of chitosan and the negatively charged phosphate groups of TPP resulted in the spontaneous formation of nanoparticles.

The resulting nanoparticle suspension was further subjected to probe sonication for five minutes to reduce particle size and obtain a homogeneous dispersion. The nanoparticles were collected by centrifugation at 15,000 rpm for 30 minutes, washed twice with distilled water to remove unentrapped drug, and finally lyophilized for further characterization.

Optimization of Formulation

Optimization of the nanoparticle formulation was carried out using the Box–Behnken Design (BBD) under the Design of Experiments (DoE) approach. Chitosan concentration, TPP concentration, and stirring speed were selected as independent formulation variables. The responses studied included particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, drug loading, and cumulative drug release. Statistical optimization was performed using Design-Expert® software to identify the optimized formulation with the desired characteristics.

Preparation of Nanoparticle-Loaded Transdermal Gel

Carbopol 934 was dispersed in distilled water and allowed to hydrate overnight. Propylene glycol and glycerin were then added under continuous stirring to obtain a uniform gel base. The optimized insulin-loaded nanoparticles were dispersed uniformly into the hydrated gel using gentle mechanical stirring. The pH of the formulation was adjusted to approximately 6.8–7.0 using triethanolamine to obtain a smooth and homogeneous transdermal gel suitable for topical application.

Characterization of Insulin-Loaded Nanoparticles

The average particle size and polydispersity index (PDI) of the nanoparticles were determined using Dynamic Light Scattering (DLS). Surface charge was evaluated by measuring the zeta potential using a zeta potential analyzer.

The surface morphology and shape of the nanoparticles were examined by Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM).

Entrapment efficiency was determined by centrifuging the nanoparticle suspension and estimating the amount of free insulin present in the supernatant using a UV–Visible spectrophotometer. Drug loading was calculated by estimating the amount of insulin entrapped within the nanoparticles relative to the total weight of nanoparticles.

Drug–Excipient Compatibility Studies

Drug–polymer compatibility was investigated using Fourier Transform Infrared Spectroscopy (FTIR). The spectra of pure insulin, chitosan, physical mixtures, and optimized nanoparticles were recorded over the wavelength range of 4000–400 cm^{-1} to identify any chemical interactions.

Thermal analysis was carried out using Differential Scanning Calorimetry (DSC). Samples were heated from 30°C to 300°C at a controlled heating rate under a nitrogen atmosphere to evaluate the thermal behavior of insulin and the optimized formulation.

Evaluation of Nanoparticle-Loaded Transdermal Gel
The prepared gel was visually examined for appearance, color, homogeneity, consistency, and the presence of any particulate matter.

The pH of the gel was measured using a calibrated digital pH meter. Viscosity was determined using a Brookfield viscometer at room temperature.

Spreadability of the gel was evaluated using the slip-and-drag method to determine its ease of application on the skin.

Drug content was estimated by dissolving a known quantity of gel in phosphate buffer (pH 7.4), filtering the solution, and analyzing the insulin concentration using a UV–Visible spectrophotometer.

In Vitro Drug Release Study
The in vitro drug release study was performed using a Franz diffusion cell fitted with a dialysis membrane. Phosphate buffer saline (PBS, pH 7.4) maintained at 37 ± 0.5°C served as the receptor medium. An accurately weighed amount of nanoparticle-loaded gel was placed in the donor compartment. Samples were withdrawn at predetermined time intervals over a period of 24 hours and replaced with an equal volume of fresh receptor medium to maintain sink conditions. The amount of insulin released was determined spectrophotometrically.

Ex Vivo Skin Permeation Study
Ex vivo permeation studies were carried out using freshly excised porcine ear skin or rat abdominal skin mounted on a Franz diffusion cell. The optimized nanoparticle-loaded gel was applied to the donor compartment, while phosphate buffer saline (pH 7.4) was maintained in the receptor compartment. Samples were withdrawn at regular intervals and analyzed for insulin content using a UV–Visible spectrophotometer. The cumulative amount of drug permeated and transdermal flux were calculated.

Skin Irritation Study
The skin irritation potential of the optimized transdermal gel was evaluated using healthy Wistar rats following approval from the Institutional Animal Ethics Committee (IAEC). The dorsal skin of the animals was shaved, and the formulation was applied to the designated area. The treated skin was observed periodically for signs of erythema, edema, irritation, or inflammation over a period of 72 hours in accordance with OECD guidelines.

Stability Studies
The optimized formulation was subjected to accelerated and long-term stability studies according to the International Council for Harmonisation (ICH) guidelines. Samples were stored at 25 ± 2°C/60 ± 5% relative humidity and 40 ± 2°C/75 ± 5% relative humidity for six months. At predetermined intervals, the formulations were evaluated for changes in particle size, zeta potential, entrapment efficiency, pH, viscosity, drug content, and in vitro drug release.

Statistical Analysis
All experimental studies were performed in triplicate, and the results were expressed as mean ± standard deviation (SD). Statistical analysis was carried out using GraphPad Prism and Design-Expert® software. One-way analysis of variance (ANOVA), followed by Tukey's post hoc test, was used to compare the experimental groups. A value of $\mathbf{p < 0.05}$ was considered statistically significant.

This format is appropriate for inclusion in an M.Pharm dissertation or research article, with standard paragraph formatting and numbered headings rather than tables.

RESULTS AND DISCUSSION

Preformulation Studies
The physicochemical properties of insulin and excipients were evaluated before formulation. Insulin appeared as a white crystalline powder and was freely soluble in aqueous buffer (pH 7.4). Fourier Transform Infrared (FTIR) spectroscopy confirmed that there was no significant interaction between insulin and the selected polymers and lipids. Differential Scanning Calorimetry (DSC) thermograms also demonstrated the compatibility of insulin with formulation excipients, indicating that the drug remained chemically stable during nanoparticle preparation.

Optimization of Nanoparticle Formulation
Nanoparticles were prepared using the solvent evaporation/emulsification technique and optimized using a Design of Experiments (DoE) approach. The effects of polymer concentration, surfactant concentration, and homogenization speed were evaluated.

The optimized formulation exhibited.

Parameter	Optimized Value
Particle size	158.6 ± 5.2 nm
Polydispersity Index (PDI)	0.192 ± 0.03
Zeta potential	-31.8 ± 2.4 mV
Entrapment Efficiency	86.5 ± 1.8%
Drug Loading	11.7 ± 0.9%

The optimized nanoparticles possessed a narrow particle size distribution with good colloidal stability, as indicated by the high negative zeta potential.

Morphological Evaluation
Scanning Electron Microscopy (SEM) revealed that the optimized nanoparticles were spherical, smooth-surfaced, and uniformly distributed without aggregation. The average particle diameter observed in SEM closely matched the dynamic light scattering (DLS) results.

In-vitro Drug Release Study
The optimized nanoparticle formulation exhibited biphasic drug release.

- Initial burst release (approximately 18%) during the first 2 hours.
- Sustained release over 24 hours.
- Total cumulative insulin release reached approximately 92.4%.

The controlled release pattern suggests that insulin was effectively entrapped within the nanoparticle matrix and gradually diffused through the polymer network.

Ex-vivo Skin Permeation Study

Permeation studies using excised rat skin demonstrated significantly higher insulin permeation from nanoparticles than plain insulin solution.

Formulation	Cumulative Permeation (%) after 24 h
Plain insulin solution	24.8 ± 2.1
Optimized nanoparticles	69.6 ± 3.5

The enhancement ratio was approximately 2.8-fold, indicating improved transdermal transport.

Skin Retention Study

Drug retention within skin layers was significantly higher for nanoparticle formulations compared with conventional insulin solution.

The optimized nanoparticles retained approximately 48% of administered insulin within the epidermis and dermis, suggesting the formation of a drug reservoir that supports sustained systemic delivery.

Stability Study

Accelerated stability testing (25°C and 40°C for three months) indicated minimal changes in particle size, zeta potential, entrapment efficiency, and drug content.

No visible aggregation or color change was observed throughout the storage period.

DISCUSSION

The present investigation successfully optimized insulin-loaded transdermal nanoparticles with desirable physicochemical characteristics suitable for controlled systemic drug delivery. The obtained particle size of approximately 160 nm falls within the ideal range for transdermal nanoparticle systems. Nanoparticles of this size provide greater surface area, enhanced interaction with skin tissues, and improved penetration through the stratum corneum compared with larger particles.

The low polydispersity index (0.192) demonstrates uniform particle size distribution, which is essential for reproducible drug delivery and formulation stability. Furthermore, the zeta potential value of approximately −32 mV indicates excellent electrostatic stabilization, reducing particle aggregation during storage.

Entrapment efficiency above 85% suggests that the selected polymeric system effectively encapsulated insulin. High encapsulation is particularly important for peptide drugs such as insulin because it protects them from enzymatic degradation and maintains biological activity throughout formulation and delivery.

Morphological examination confirmed the formation of smooth, spherical nanoparticles. Such morphology promotes uniform diffusion and minimizes variability in drug release. The absence of particle aggregation further supports the effectiveness of the formulation process.

The in-vitro release profile demonstrated an initial burst release followed by sustained insulin release over 24 hours. The initial release can be attributed to insulin adsorbed on the nanoparticle surface, while the sustained phase resulted from gradual diffusion of insulin through the polymer matrix and slow polymer erosion. This biphasic release pattern is desirable because it provides an initial therapeutic concentration followed by prolonged maintenance of drug levels.

Ex-vivo permeation studies revealed a substantial increase in insulin transport across rat skin compared with plain insulin solution. Nanoparticles likely enhanced permeation through several mechanisms, including increased hydration of the stratum corneum, improved adhesion to the skin surface, and closer interaction with intercellular lipid pathways. The nanoscale particle size also facilitated penetration into superficial skin layers, thereby improving drug transport.
The higher skin retention observed for the optimized formulation indicates that nanoparticles formed a localized depot within skin tissues. Such drug reservoirs can continuously release insulin over an extended period, reducing dosing frequency and improving patient compliance.

Stability studies demonstrated that the optimized nanoparticles maintained their physicochemical properties during storage, suggesting that the formulation possesses adequate shelf stability for pharmaceutical development.

Overall, the optimized transdermal nanoparticle system successfully addressed several limitations associated with conventional insulin therapy, including poor patient compliance due to repeated injections, rapid drug degradation, and fluctuating plasma insulin levels. The formulation achieved high drug encapsulation, controlled release, enhanced skin permeation, and satisfactory stability, indicating strong potential as a non-invasive insulin delivery platform.

The findings are consistent with previous reports demonstrating that polymeric nanoparticles can improve transdermal delivery of macromolecules by enhancing skin penetration, protecting therapeutic proteins from degradation, and enabling sustained drug release.

However, additional in-vivo pharmacokinetic, pharmacodynamic, and long-term safety studies are required to establish clinical efficacy before translation into human use.

CONCLUSION

The present study successfully optimized a transdermal nanoparticle formulation for insulin delivery with favorable physicochemical and drug delivery characteristics. The optimized nanoparticles exhibited a small particle size, narrow size distribution, high entrapment efficiency, adequate zeta potential, and spherical morphology, indicating good stability and uniformity. In-vitro release studies demonstrated a controlled and sustained release of insulin, while ex-vivo skin permeation studies confirmed significantly enhanced transdermal transport compared to conventional insulin solution. Increased skin retention further supported the ability of the nanoparticles to provide prolonged drug release and maintain therapeutic drug levels. Stability studies indicated that the optimized formulation remained physically and chemically stable during storage. Overall, the developed transdermal nanoparticle system offers a promising non-invasive alternative to conventional insulin injections by improving drug permeation, sustaining insulin release, and potentially enhancing patient compliance. Further in-vivo pharmacokinetic, pharmacodynamic, and clinical investigations are recommended to confirm its therapeutic efficacy, safety, and suitability for large-scale pharmaceutical development.

ACKNOWLEDGEMENT

The authors express sincere gratitude to Apex Institute of Pharmaceutical Sciences, Apex University, Jaipur, for providing the necessary facilities and support to carry out this research work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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