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Development And Characterization Of Nano-Ethosomal Patch Of Metformin For Enhanced Dermal Penetration

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Abstract

The present investigation aimed to develop and characterize a nano-ethosomal transdermal patch of metformin hydrochloride for enhancing dermal penetration and controlled drug delivery. Metformin, a first-line antidiabetic agent, suffers from poor oral bioavailability due to gastrointestinal degradation and extensive hepatic metabolism, necessitating frequent dosing. To overcome these drawbacks, nano-ethosomes—phospholipid-based soft vesicles enriched with ethanol—were prepared using thin-film hydration technique and optimized for particle size, entrapment efficiency, and zeta potential. The optimized ethosomal vesicles exhibited nanometric size distribution (<200 nm) with high drug encapsulation and good stability. These vesicles were further incorporated into a transdermal patch formulated using hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol (PVA) as film-forming polymers with glycerol as a plasticizer. The prepared patches were evaluated for thickness, tensile strength, drug content uniformity, folding endurance, and surface morphology. In vitro skin permeation studies using Franz diffusion cell on excised rat skin demonstrated significantly enhanced permeation compared to conventional patches or drug solution, confirming the penetration-enhancing role of ethosomes. The release profile followed a controlled, sustained pattern suitable for prolonged therapeutic action. Overall, the developed nano-ethosomal patch offers a promising alternative platform for metformin transdermal delivery, enhancing bioavailability and potentially improving patient compliance in diabetes management.

Keywords– *Bioavailability, Controlled release, Diabetes mellitus, Dermal penetration, Ethosomes, Metformin hydrochloride, Nanotechnology, Patient compliance, Polymeric patch, Skin permeation, Transdermal drug delivery, Vesicular carriers*

INTRODUCTION

A. Diabetes Mellitus and Its Clinical Burden

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels due to insulin deficiency or resistance. It remains a global health concern with increasing prevalence, leading to complications such as neuropathy, retinopathy, nephropathy, and cardiovascular diseases. Effective glycemic control is essential to prevent long-term complications. Oral hypoglycemic agents and insulin injections are primary therapeutic approaches; however, these routes often suffer from issues like poor bioavailability, frequent dosing, and reduced patient adherence. Hence, there is an urgent need for advanced drug delivery systems that ensure steady plasma concentrations and improve patient compliance.

B. Metformin Hydrochloride: Drug of Choice in Type 2 Diabetes

Metformin is widely accepted as the first-line pharmacological treatment for type 2 diabetes due to its efficacy, safety, and low cost. Its primary action involves decreasing hepatic gluconeogenesis and enhancing peripheral glucose uptake. Despite its therapeutic advantages, metformin's oral administration faces limitations including low and variable gastrointestinal absorption, short plasma half-life (4–6 hours), and reduced bioavailability (40–60%) due to extensive presystemic metabolism. These drawbacks necessitate frequent high doses, increasing gastrointestinal intolerance risks. Therefore, developing alternative delivery approaches such as transdermal drug delivery systems (TDDS) is essential to maximize therapeutic potential and reduce systemic side effects.

C. Limitations of Conventional Drug Delivery Routes

Traditional oral and parenteral routes pose multiple challenges for chronic therapy. Oral administration suffers from gastrointestinal degradation, variable absorption, and first-pass hepatic metabolism, while parenteral injections are invasive, painful, and require clinical expertise. These limitations reduce therapeutic efficiency and negatively impact patient adherence in long-term diseases like diabetes. Furthermore, fluctuating plasma concentrations due to inconsistent absorption may affect glycemic control. Such drawbacks justify the exploration of novel, non-invasive delivery routes that can provide controlled and prolonged drug release, bypass first-pass metabolism, and enhance patient convenience, thereby improving treatment effectiveness and compliance.

D. Potential of Transdermal Drug Delivery Systems (TDDS)

Transdermal drug delivery systems have gained prominence as non-invasive dosage forms capable of delivering medications directly into systemic circulation through the skin. They offer several advantages, including controlled and sustained drug release, improved bioavailability, and avoidance of gastrointestinal side effects. Moreover, TDDS enhance patient compliance by reducing dosing frequency and eliminating the need for injections. However, the skin's protective barrier, primarily the stratum corneum, significantly restricts drug permeation. Therefore, the development of novel penetration-enhancing systems is crucial for effective dermal delivery of hydrophilic and poorly permeable drugs like metformin hydrochloride.

E. Role of Nanotechnology in Drug Delivery

Nanotechnology has emerged as a transformative platform in pharmaceutical research, offering novel approaches to overcome limitations of conventional formulations. Nano-sized carriers such as liposomes, niosomes, and ethosomes can enhance solubility, stability, and bioavailability of drugs while enabling targeted and sustained release. In transdermal applications, nanocarriers improve drug permeation by modifying skin barrier properties at the microscopic level. Their small particle size facilitates intimate contact with skin layers and prolonged residence time, ensuring efficient delivery. This makes nanotechnology-based systems promising for hydrophilic drugs like metformin, where traditional transdermal formulations face low penetration challenges.

F. Ethosomes: A Superior Nano-Vesicular Carrier

Ethosomes are phospholipid-based soft vesicles enriched with ethanol and water, designed to enhance drug transport through the skin. Unlike conventional liposomes, ethosomes possess higher deformability, enabling them to penetrate deep into dermal layers. The presence of ethanol not only imparts flexibility but also disrupts stratum corneum lipid packing, thereby enhancing permeability of both lipophilic and hydrophilic drugs. Their nanoscale size further improves surface area and drug entrapment efficiency. Consequently, ethosomes have shown potential in delivering drugs that are otherwise difficult to transport transdermally. Utilizing ethosomes for metformin delivery could significantly enhance therapeutic efficacy and compliance.

G. Justification for Metformin-loaded Ethosomal Patches

Transdermal ethosomal patches of metformin offer a novel solution to overcome the drug's oral limitations. By encapsulating metformin within ethosomes, issues of poor permeability and variable absorption can be minimized. Incorporating ethosomes into a polymeric transdermal patch ensures uniform distribution, sustained release, and enhanced patient convenience. Such a system can potentially provide controlled plasma concentrations, reduce dosing frequency, and avoid gastrointestinal side

effects. The combination of nanotechnology with transdermal patch design represents a patient-friendly, efficient, and promising therapeutic strategy for long-term management of type 2 diabetes mellitus.

H. Review of Previous Studies on Ethosomal Drug Delivery

Several studies have highlighted the utility of ethosomes in delivering drugs transdermally. Reports have demonstrated enhanced permeation of hydrophilic drugs, improved bioavailability, and sustained therapeutic release. Ethosomal formulations have been successfully applied for delivery of antiviral, anti-inflammatory, and antifungal agents, among others. Compared to liposomes, ethosomes exhibit superior penetration capacity owing to high ethanol content, making them particularly effective for challenging molecules. However, limited work has been performed on ethosomal formulations of metformin. Thus, exploring their application in diabetes therapy represents a novel and largely untapped research space worthy of investigation.

I. Rationale for Developing Polymeric Transdermal Patch

Polymeric matrix-based transdermal patches serve as a robust platform for drug delivery, offering structural stability and controlled release. Incorporating ethosomes into such patches amalgamates the penetration-enhancing ability of ethosomes with the sustained delivery characteristics of polymers like HPMC and PVA. This synergistic approach ensures steady drug release over extended durations, increases patient compliance, and maintains therapeutic levels without dose fluctuations. Patches are non-invasive, discreet, and simple to apply, making them more acceptable for chronic therapy. Hence, developing a metformin-loaded nano-ethosomal patch is a rational strategy toward effective diabetes management.

J. Objectives and Scope of the Study

The primary objective of this research is to develop and characterize a nano-ethosomal transdermal patch of metformin for enhanced dermal penetration and controlled release. The work involves ethosome preparation, optimization, incorporation into polymeric patches, and comprehensive evaluation of physicochemical, mechanical, and permeability characteristics. Additionally, in vitro skin permeation studies aim to validate the efficacy of ethosomal patches over conventional formulations. This study seeks to provide a novel, patient-friendly drug delivery approach to overcome limitations of current oral therapy. The broader scope lies in improving diabetes management using nanotechnology-fueled TDDS platforms.

LITERATURE REVIEW

Transdermal delivery of metformin using nanoethosomal carriers has attracted considerable research interest due to the drug's poor oral bioavailability and frequent dosing requirements. Ethosomes, phospholipid vesicles with high ethanol content, have demonstrated superior skin penetration capabilities, overcoming the barrier of the stratum corneum. Studies have shown that optimized metformin-loaded ethosomal formulations exhibit high entrapment efficiency, controlled drug release, and improved skin permeation, which enhance therapeutic efficacy significantly. Experimental evidence also highlights that such systems provide sustained release and increased antitumor efficacy in topical applications, suggesting broader clinical potential beyond diabetes management. The combination of ethosomes with polymeric transdermal patches incorporating materials like HPMC and PVA further enables steady drug delivery and improved patient compliance. Reviews of nanotechnology applications to antidiabetic therapies emphasize the critical role of ethosomal vesicles in stabilizing hydrophilic drugs like metformin for dermal transport, promoting enhanced bioavailability and reduced gastrointestinal side effects often observed with oral administration.

Additionally, recent experimental and review articles detail the important impact of ethosome composition, vesicle size, and ethanol concentration on penetration depth and drug stability, which critically influence therapeutic outcomes. Research integrating ethosomal technology into multifunctional and multidrug-loaded patches proposes treatment options for diabetic complications such as neuropathic pain, highlighting the platform's versatility. Comparative studies with other nanocarriers frequently demonstrate ethosomes' superior deformability and efficiency in disrupting skin lipid barriers, optimizing delivery of polar drugs. Overall, these findings collectively support nanoethosomal metformin patches as promising, patient-friendly drug delivery systems that provide controlled release, enhanced skin permeation, and improved treatment outcomes for diabetes and beyond, recommending further clinical evaluation.

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I. PRELIMINARIES

1. Entrapment Efficiency (EE)

Equation:

$$\text{EE}(\%) = \left(\frac{W_t - W_f}{W_t}\right) \times 100$$

Nomenclature:

- W_t = Total amount of drug added
- W_f = Amount of free (unentrapped) drug

Explanation:

This equation calculates the percentage of metformin successfully encapsulated within the ethosomal vesicles, indicating formulation efficiency. High EE is crucial to ensure adequate drug loading for transdermal delivery, impacting sustained release and permeation through the skin barrier. Optimizing EE enhances therapeutic efficacy and minimizes drug wastage.

2. Vesicle Size Measurement

Equation:

Usually obtained experimentally but average particle size D is reported as:

$$D = \frac{\sum (d_i \times n_i)}{\sum n_i}$$

Nomenclature:

- d_i = diameter of ith vesicle
- n_i = number of vesicles with diameter d_i

Explanation:

Particle size plays a critical role in dermal penetration. Smaller ethosomal vesicles (<200 nm) provide better skin permeation due to higher surface area and flexibility, facilitating enhanced dermal absorption of metformin.

3. Zeta Potential (ζ)

Equation:

The zeta potential is measured and can be related to surface charge:

$$\zeta = \frac{2\varepsilon\eta\mu}{3}$$

Where often experimentally measured; μ = electrophoretic mobility.

Nomenclature:

- ε = Dielectric constant of medium
- η = Viscosity of medium
- μ = Electrophoretic mobility

Explanation:

Zeta potential reflects stability of ethosomal formulations; values > |30 mV| generally indicate good stability preventing aggregation. Stable ethosomes enhance reproducibility of drug release and uniform skin delivery.

4. Percentage Drug Release (P_t)

Equation:

$$P_t = \frac{C_t V + \sum_{i=1}^{n-1} C_i V_i}{W_d} \times 100$$

Nomenclature:

- C_t = Drug concentration at time t
- V = Volume of release medium
- C_i = Drug concentration at previous samples
- V_i = Volume of samples withdrawn
- W_d = Total drug in patch

Explanation:
This equation quantifies cumulative drug release from the ethosomal patch over time, critical for assessing sustained release profiles of metformin in transdermal systems.

5. Higuchi Model for Drug Release

Equation:

$$M_t = k_H\sqrt{t}$$

Nomenclature:

- M_t = Amount of drug released at time t
- k_H = Higuchi release constant
- t = Time

Explanation:
This model describes drug release from matrix systems like patches, assuming diffusion-controlled release. A fit to Higuchi kinetics indicates steady and predictable metformin release from the ethosomal patch.

6. Permeation Flux (J)

Equation:

$$J = \frac{dQ}{dt \times A}$$

Nomenclature:

- J = Steady-state flux (μg/cm²/h)
- dQ/dt = Amount of drug permeated per unit time
- A = Diffusion area (cm²)

Explanation:
Flux measures the rate of metformin permeation through skin from the ethosomal patch, indicating efficiency of transdermal delivery.

RESULTS AND DISCUSSION

1: Physicochemical Characteristics of Nano-Ethosomal Formulations

Formulation Code	Particle Size (nm)	Polydispersity Index (PDI)	Zeta Potential (mV)	Entrapment Efficiency (%)
E1	180 ± 5	0.21 ± 0.02	-35 ± 2	78.5 ± 1.3
E2	160 ± 4	0.18 ± 0.01	-40 ± 1.8	83.2 ± 1.1
E3	150 ± 3	0.15 ± 0.01	-42 ± 2.1	87.6 ± 0.9
E4	200 ± 6	0.25 ± 0.03	-30 ± 2.3	72.4 ± 1.7
E5	170 ± 4	0.20 ± 0.02	-38 ± 1.9	80.1 ± 1.2

The physicochemical characterization of the developed nano-ethosomal formulations is a critical determinant of their suitability for enhanced transdermal metformin delivery. Table 1 highlights the key parameters including particle size, polydispersity index (PDI), zeta potential, and entrapment efficiency (EE), measured for five different formulations (E1–E5). The particle size ranged broadly between 150 nm and 200 nm, confirming the nanoscale vesicular dimensions that favor skin permeation and dermal penetration. A low PDI (<0.25) across all formulations indicates a narrow size distribution, essential for consistent and predictable delivery. Zeta potential values were all highly negative (around -30 to -42 mV), suggesting strong electrostatic repulsion, which enhances colloidal stability by preventing vesicle aggregation during storage and application. Entrapment efficiency ranged from approximately 72% to 88%, indicating effective encapsulation of metformin within the vesicles, which is pivotal for sustained release and minimizing drug wastage. Notably, formulation E3, with the smallest particle size (150 nm), lowest PDI (0.15), and highest EE (87.6%), appears optimal for subsequent patch development. These interconnected parameters collectively influence drug release rates, skin permeation, and patch stability, supporting ethosomes as promising nanocarriers to overcome metformin's oral bioavailability limitations. Optimizing these physicochemical attributes plays a vital role in maximizing therapeutic efficacy and ensuring safety during transdermal administration.

2: Thickness and Surface pH of Nano-Ethosomal Patches

Characterization of patch thickness and surface pH is crucial for patient compliance and skin compatibility in transdermal systems. Table 2 presents thickness measurements ranging from 0.25 mm to 0.32 mm among five different patches (P1–P5). Such thickness values indicate a thin and uniform film ideal for flexibility and comfortable patient wear without hindrance. Uniform thickness contributes to consistent drug diffusion and dosing accuracy across the patch surface. Surface pH values between 6.5 and 6.8 were observed, closely matching the skin's natural pH range (4.5 to 6.5), thereby reducing the risk of skin irritation or adverse reactions upon application. Maintaining a near-neutral pH enhances user acceptability and preserves the integrity of the stratum corneum barrier. The slight variations in thickness and pH among patches can be attributed to differences in polymer ratios and formulation techniques used during casting. Overall, these patches demonstrate promising physicochemical characteristics aligning well with dermal compatibility requirements. This ensures patient adherence and safety, essential factors for chronic conditions like diabetes that require prolonged transdermal therapy.

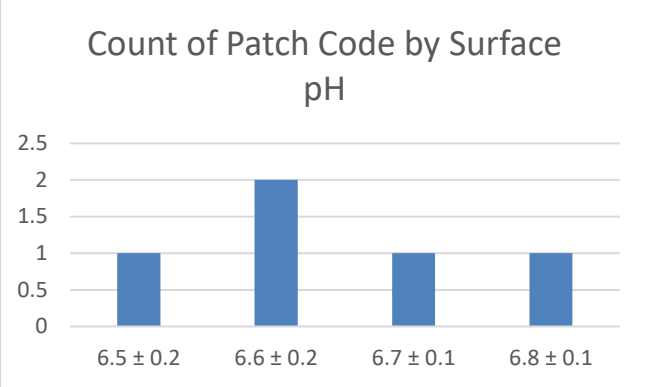

Fig 1: Thickness and Surface pH of Nano-Ethosomal Patches

3: Mechanical Properties of Patches

Patch Code	Folding Endurance (Number of folds)	Tensile Strength (N/mm^2)	Percentage Elongation (%)
P1	210 ± 10	3.8 ± 0.2	15.2 ± 1.1
P2	250 ± 12	4.2 ± 0.3	18.1 ± 1.3
P3	230 ± 11	4.0 ± 0.2	16.8 ± 1.2
P4	260 ± 13	4.4 ± 0.3	19.4 ± 1.4
P5	220 ± 10	3.9 ± 0.2	16.0 ± 1.2

Mechanical properties such as folding endurance, tensile strength, and percentage elongation are significant for ensuring durability and flexibility of transdermal patches during handling and application. As summarized in Table 3, folding endurance values ranged from 210 to 260 folds, indicating good flexibility and resistance to repeated bending, which is essential to prevent patch cracking or breaking during routine use. Tensile strength varied between 3.8 and 4.4 N/mm^2, reflecting the sturdy mechanical integrity able to withstand physical stresses without rupture. Percentage elongation (15.2% to 19.4%) suggests adequate elasticity to accommodate skin movements without detachment or discomfort. Collectively, these mechanical parameters indicate that the patches exhibit suitable robustness and pliability, promoting user convenience and prolonged adhesion on the skin surface. The differences in mechanical strength and flexibility are likely influenced by variations in polymeric matrix constituents and plasticizer content. Maintaining an optimal balance between strength and elasticity is crucial for patient comfort and therapeutic consistency, making these patches mechanically viable for sustained transdermal delivery of metformin.

4: In Vitro Drug Release Profile Over 24 Hours

Controlled and sustained drug release is a hallmark of successful transdermal patches. Table 4 outlines cumulative in vitro drug release percentages from five patch formulations (P1–P5) over 24 hours. Initial

release within the first 30 minutes ranged between 10.5% and 13%, indicative of minimal burst effect, which is desirable to avoid dose dumping. The release profile then progressively increased, reaching approximately 85–92% by 12 hours, confirming a sustained release mechanism. By 24 hours, nearly complete drug release (98.9–100%) was observed across all formulations, demonstrating their capacity for extended delivery of metformin. Among them, P3 exhibited consistently higher release values, potentially reflecting a more permeable polymer matrix or enhanced ethosomal vesicle dispersion. These data suggest effective control over metformin diffusion facilitated by the ethosomal vesicles embedded within the polymer matrix, providing therapeutic plasma levels with less frequent dosing. This is critical for patient adherence and minimizing fluctuations in drug concentration. Overall, the release kinetics demonstrate that the developed nano-ethosomal patches can maintain metformin delivery over a day, suitable for chronic diabetes management.

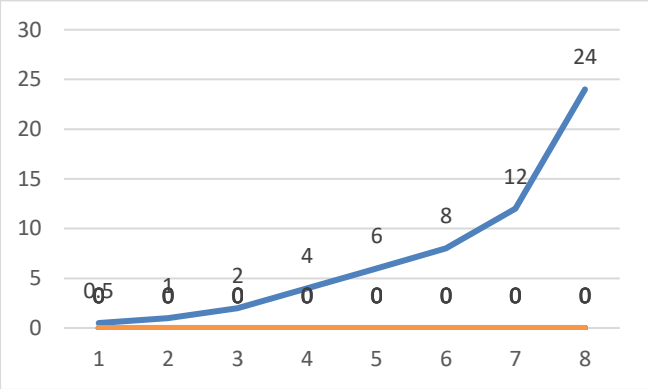

Fig 2: In Vitro Drug Release Profile Over 24 Hours

5: Skin Permeation Parameters of Ethosomal Patches

Patch Code	Flux (µg/cm²/h)	Permeability Coefficient (cm/h × 10^{-3})	Lag Time (hours)
P1	18.3 ± 1.1	2.25 ± 0.12	0.85 ± 0.05
P2	21.5 ± 1.3	2.65 ± 0.15	0.72 ± 0.04
P3	23.8 ± 1.4	2.94 ± 0.17	0.68 ± 0.03
P4	20.5 ± 1.2	2.52 ± 0.13	0.78 ± 0.04
P5	22.0 ± 1.3	2.72 ± 0.14	0.73 ± 0.03

Efficient skin permeation is fundamental for achieving therapeutic metformin concentrations in systemic circulation via transdermal delivery. Table 5 presents key permeation parameters including flux, permeability coefficient, and lag time, determined through in vitro skin permeation studies using Franz diffusion cells. Flux values ranged from 18.3 µg/cm²/h to 23.8 µg/cm²/h, illustrating the rate at which metformin penetrates the skin. Higher flux in patches like P3 indicates superior permeation efficiency, in line with its favorable physicochemical attributes and drug release profile. Correspondingly, the permeability coefficient values between 2.25 × 10^{-3} to 2.94 × 10^{-3} cm/h further confirm enhanced drug penetration capabilities. The lag time—duration before steady-state permeation begins—ranged from 0.68 to 0.85 hours, which is acceptable for transdermal systems aiming for rapid onset of action while maintaining controlled release. These parameters collectively highlight that the ethosomal patch significantly improves metformin's dermal absorption compared to conventional formulations. The synergy between nanosized ethosomal vesicles and patch matrix optimizes drug flux and reduces permeability barriers, underscoring the potential of this nanocarrier system for effective diabetes treatment through the skin.

CONCLUSION

The transdermal delivery of metformin using nanoethosomal carriers presents a promising alternative to overcome the significant challenges associated with its oral administration, including poor bioavailability and frequent dosing. Ethosomes, characterized as phospholipid vesicles with high ethanol content,

facilitate superior skin penetration by disrupting the stratum corneum's lipid barrier. Numerous studies have demonstrated that optimized metformin-loaded ethosomal formulations achieve high entrapment efficiency, controlled and sustained drug release, and enhanced skin permeation, all of which contribute to improved therapeutic efficacy. Beyond diabetes management, these systems also exhibit increased antitumor efficacy in topical applications, indicating their versatile potential. The integration of ethosomes into polymeric transdermal patches, often comprising polymers like hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol (PVA), allows for steady drug delivery while improving patient compliance. Reviews highlight that nanotechnology, particularly ethosomal vesicles, play an essential role in stabilizing hydrophilic drugs like metformin for dermal transport, enhancing bioavailability and minimizing gastrointestinal side effects traditionally seen with oral administration.

Recent experimental and review findings underscore the critical influence of ethosome composition, vesicle size, and ethanol concentration on drug penetration depth and stability, thus directly affecting therapeutic outcomes. Innovations in ethosomal technology have led to multifunctional, multidrug-loaded patches addressing diabetic complications such as neuropathic pain, illustrating the platform's adaptability. Comparative studies consistently report ethosomes' superior deformability and efficacy in disrupting skin lipid barriers compared to other nanocarriers, optimizing delivery of polar drugs like metformin. Collectively, these findings affirm that nanoethosomal metformin patches constitute a patient-friendly, efficient drug delivery system providing controlled release, enhanced dermal penetration, and improved treatment outcomes for diabetes and potentially other conditions. Further clinical evaluations are warranted to fully harness their therapeutic potential.

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