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FORMULATION AND EVALUATION OF TRANSDERMAL MATRIX PATCHES OF BIGUANIDES FOR ENHANCED DRUG DELIVERY

Abhinav Jain[1]*, Dr Sachin Kumar Jain[2]

[1]Research Scholar, Faculty of Pharmacy, Oriental University, Indore, Madhya Pradesh.

[2]Principal, Faculty of Pharmacy, Oriental University, Indore, Madhya Pradesh.

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Corresponding Author: Abhinav Jain

Address: Research Scholar, Faculty of Pharmacy, Oriental University, Indore, Madhya Pradesh.

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ABSTRACT

Transdermal drug delivery systems (TDDS) offer a promising alternative to conventional drug administration by providing controlled drug release, improved bioavailability, and enhanced patient compliance. The present study aimed to develop and evaluate matrix-type transdermal patches of metformin hydrochloride for sustained drug delivery in the management of diabetes mellitus. Transdermal patches were prepared using the solvent evaporation method with ethyl cellulose (EC) and polyvinylpyrrolidone (PVP K-30) in varying ratios, employing dibutyl phthalate as a plasticizer. Various permeation enhancers, including dimethyl sulfoxide (DMSO), Tween-80, eucalyptus oil, and olive oil, were incorporated at different concentrations. The prepared patches were evaluated for physicochemical properties such as thickness, weight variation, drug content, moisture content, flatness, and tensile strength. In vitro drug release studies were performed using USP dissolution apparatus, while ex vivo permeation studies were conducted using excised rat skin in a Franz diffusion cell. Stability studies were carried out as per ICH guidelines. The formulated patches exhibited satisfactory physicochemical characteristics with uniform drug distribution (96.23–98.89%). Among all formulations, F3 (EC: PVP 3:2) showed optimal mechanical properties and sustained drug release. The incorporation of permeation enhancers significantly improved drug release and permeation, with FT1 (2% Tween-80) showing maximum drug release (98.89%) and highest flux (32.89 µg/cm²/h). Drug release followed

Higuchi and Korsmeyer–Peppas kinetics, indicating diffusion-controlled, non-Fickian transport. Stability studies confirmed that the optimized formulation remained stable under accelerated conditions. In conclusion, the developed transdermal matrix patch of metformin hydrochloride demonstrated sustained drug release, enhanced permeation, and improved stability, suggesting its potential as an effective alternative to conventional oral therapy for diabetes management.

KEYWORDS: Transdermal drug delivery, Metformin hydrochloride, Matrix patch, Permeation enhancers, Sustained release, Diabetes mellitus.

1. INTRODUCTION

Transdermal drug delivery systems (TDDS) are designed to deliver drugs across the skin into systemic circulation at a controlled rate, thereby maintaining therapeutic drug levels for extended periods. This route offers a non-invasive alternative to oral and parenteral administration by avoiding first-pass metabolism and gastrointestinal degradation, while also improving patient compliance. Additionally, therapy can be easily terminated by removing the patch, thereby reducing the risk of toxicity.

Since the approval of the first scopolamine transdermal patch in 1979, TDDS has gained considerable attention. Currently available systems include drugs such as nicotine, nitroglycerin, clonidine, fentanyl, testosterone, and estradiol. The global transdermal market continues to expand due to the increasing demand for controlled drug delivery and improved therapeutic outcomes.

The skin, the largest organ of the body, acts as the primary barrier to drug permeation. It consists of three layers: epidermis, dermis, and hypodermis. The outermost layer, the stratum corneum, serves as the principal barrier due to its highly organized lipid–protein structure. Drug permeation occurs through three main pathways: transcellular, intercellular, and transfollicular routes.

TDDS offers several advantages, including enhanced bioavailability, reduced dosing frequency, minimized side effects, and improved patient adherence. However, limitations such as skin irritation and restricted drug permeability remain significant challenges.

Various formulation strategies have been developed to optimize transdermal delivery, including membrane-controlled, matrix-type, adhesive diffusion-controlled, and

microreservoir systems. Key components of TDDS include polymers, drugs, permeation enhancers, adhesives, backing membranes, and release liners. The selection of suitable drug candidates is critical, with ideal properties including low molecular weight, balanced lipophilicity, and adequate solubility.

Permeation enhancers such as dimethyl sulfoxide, azone, fatty acids, and terpenes are commonly employed to improve drug transport across the skin by modifying the stratum corneum barrier.

In conclusion, TDDS represents a promising and evolving approach for drug delivery, particularly for chronic and central nervous system disorders, offering significant therapeutic and patient compliance advantages.

2. Objective of the Present Study

The present study aims to develop a transdermal drug delivery system (TDDS) of metformin for sustained and controlled drug release, with the goal of reducing dose-related side effects and improving patient compliance in diabetic patients.

The specific objectives are:

- To formulate matrix-type transdermal patches of metformin
- To evaluate physicochemical properties such as thickness, weight uniformity, drug content, moisture content, folding endurance, tensile strength, and pH
- To perform in vitro drug release studies
- To investigate the effect of different permeation enhancers
- To conduct in vitro permeation studies using excised rat skin and a Franz diffusion cell
- To assess in vivo skin irritation of optimized formulations
- To evaluate therapeutic efficacy through animal studies
- To perform stability studies as per ICH guidelines
- To analyze data using appropriate statistical methods

3. MATERIALS AND METHODS (Preformulation and Evaluation)

3.1 Preformulation Studies

Preformulation studies were conducted to characterize the physicochemical properties of metformin and ensure compatibility with formulation components.

Metformin hydrochloride was obtained as a white to off-white, odorless crystalline powder. The melting point was determined using the capillary method. Drug identity was confirmed by FT-IR spectroscopy (4000–450 cm^{-1}). Solubility studies were performed in various solvents to select suitable media for drug release and permeation studies.

3.1.1 Formulation of Transdermal Patches

Matrix-type transdermal patches were prepared by the solvent evaporation method using ethyl cellulose (EC) and polyvinylpyrrolidone (PVP K-30) in varying ratios. Dibutyl phthalate (30% w/w) was used as a plasticizer, and metformin (20% w/w) was incorporated into the polymeric solution.

The optimized polymer ratio (EC:PVP = 3:2) was further formulated with permeation enhancers (DMSO, Tween-80, eucalyptus oil, and olive oil) at concentrations of 2%, 5%, and 10% w/w. The solution was cast in Petri dishes and dried at room temperature for 24 h to obtain uniform films.

3.2 Evaluation of Transdermal Patches

The prepared patches were evaluated for the following parameters:

- **Physical appearance:** color, clarity, smoothness, and flexibility
- **Thickness:** measured using a digital thickness gauge
- **Weight variation:** determined using a digital balance
- **Drug content:** analyzed by UV spectrophotometry at 227 nm
- **Moisture content and uptake:** evaluated using desiccator methods
- **Flatness:** assessed by measuring dimensional uniformity
- **Tensile strength:** determined using a customized assembly

3.2.1 In Vitro Drug Release

Drug release studies were performed using USP dissolution apparatus (Type II) at 32 ± 0.5°C in phosphate buffer (pH 7.4) containing 20% methanol. Samples were withdrawn at predetermined intervals up to 24 h and analyzed spectrophotometrically.

4.2.2 Stability Studies

Stability studies were conducted as per ICH guidelines at 40°C and 75% RH for 3 months. Samples were evaluated at 30, 60, and 90 days for physical appearance and drug content.

3.2.3 Statistical Analysis

Data were analyzed using one-way ANOVA followed by appropriate post hoc tests, with significance considered at $p < 0.05$.

4. RESULTS AND DISCUSSION

4.1 Preformulation Studies

Metformin hydrochloride was confirmed as a white, crystalline, odorless, bitter drug consistent with pharmacopoeial standards. The melting point (223.3 ± 0.58°C) matched reported values, indicating purity. FT-IR spectra confirmed characteristic functional groups with no drug– excipient interaction. The drug showed highest solubility in methanol and adequate solubility in 20% methanol–PBS (pH 7.4), selected for further studies.

4.2 Formulation of Transdermal Patches

Matrix-type patches were prepared using EC and PVP in varying ratios. The optimized polymer ratio (3:2) was selected based on preliminary evaluation. Permeation enhancers (Tween-80, DMSO, eucalyptus oil, olive oil) were incorporated at 2%, 5%, and 10%.

4.3 Physicochemical Evaluation

All patches were uniform, flexible, and smooth. Thickness (0.28–0.39 mm) and weight variation indicated reproducibility. Drug content ranged from 96.23–98.89%, confirming uniform distribution. Moisture content and uptake increased with PVP due to its hydrophilicity. High flatness (>98%) and adequate tensile strength were observed, with F3 showing optimal mechanical properties.

4.4 Optimization of Polymer Ratio

Formulation F3 (EC:PVP 3:2) exhibited optimal flexibility, drug content (98.67%), moderate moisture uptake, and sufficient tensile strength, and was selected for further studies.

4.5 Calibration Curve

A linear calibration curve (R^2 = 0.9998) was obtained at 227 nm, confirming method reliability for drug quantification.

4.6 In Vitro Drug Release (F1–F5)

Drug release increased with PVP content. F3 showed optimal sustained release (96.78% at 24 h), while F1 showed slowest release due to hydrophobic EC.

4.7 Effect of Permeation Enhancers

All enhancers improved drug release. Maximum release was observed with:

- **FT1 (2% Tween-80): 98.89%**
- **FT10 (2% Olive oil): 98.78%**

Higher concentrations did not significantly enhance release.

4.8 Comparative Release

Release order:

FT1 > FT10 > FT4 > FT7 > F3

Tween-80 and olive oil were the most effective enhancers.

4.9 Drug Release Kinetics

Drug release followed Higuchi and Korsmeyer–Peppas models, indicating diffusion-controlled, non-Fickian (anomalous) transport.

4.10 Ex Vivo Permeation

FT1 showed highest flux (32.89 µg/cm²/h) and enhancement ratio (1.22) with reduced lag time. Enhancers improved permeation by modifying stratum corneum properties.

4.11 Optimized Formulation

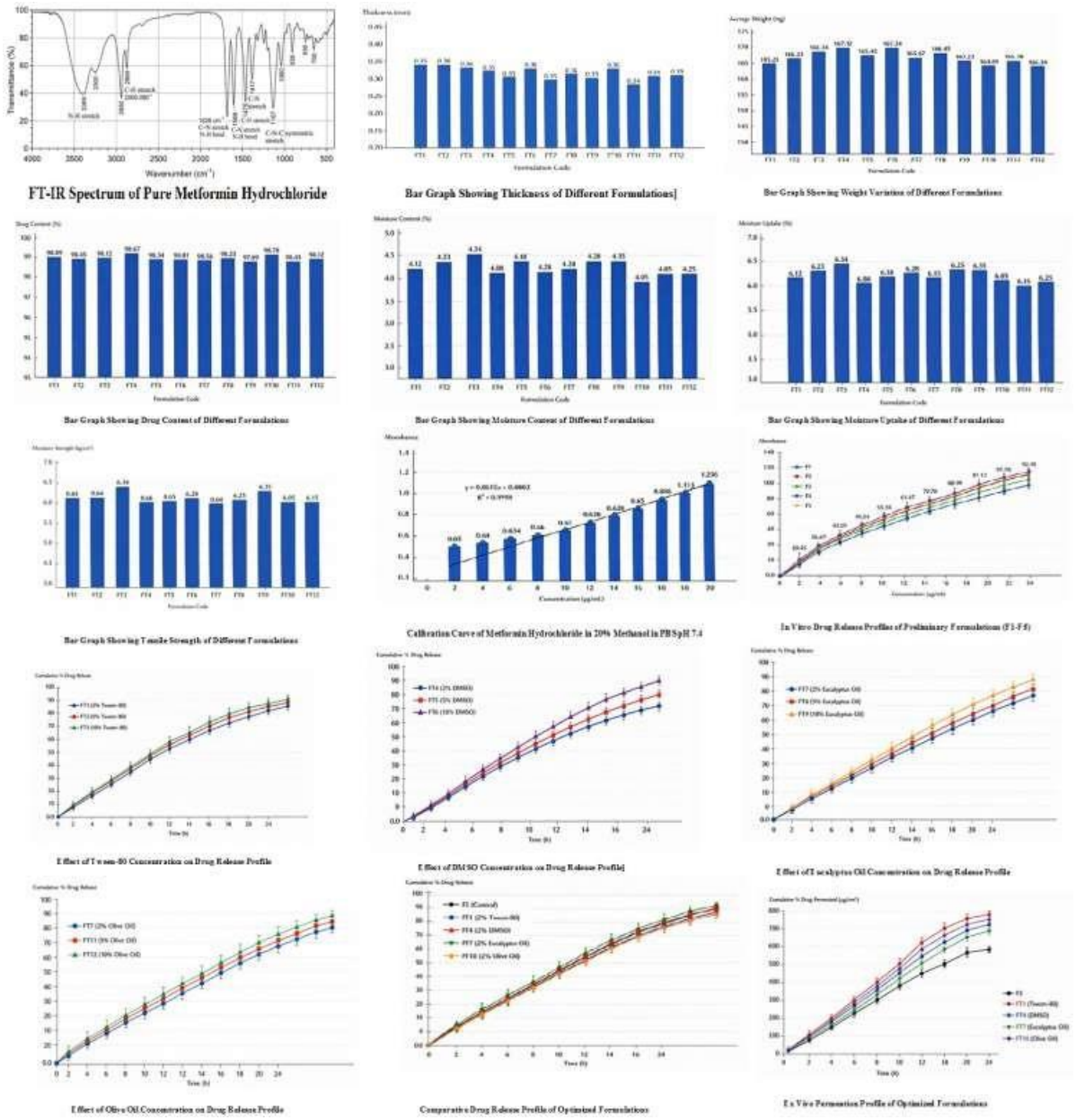
FT1 (2% Tween-80) was selected based on superior drug release, permeation, and physicochemical properties.

4.12 Stability Studies

FT1 remained stable over 3 months with negligible drug degradation and no change in physical properties.

4.13 Statistical Analysis

Statistical analysis confirmed significant improvement in drug release and permeation for FT1 and FT10 ($p < 0.01$ to $p < 0.001$).



FT-IR Spectrum of Pure Metformin Hydrochloride

Bar Graph Showing Thickness of Different Formulations]

Bar Graph Showing Weight Variation of Different Formulations

Bar Graph Showing Drug Content of Different Formulations

Bar Graph Showing Moisture Content of Different Formulations

Bar Graph Showing Moisture Uptake of Different Formulations

Bar Graph Showing Tensile Strength of Different Formulations

Calibration Curve of Metformin Hydrochloride in 20% Methanol in PBS pH 7.4

In Vitro Drug Release Profiles of Preliminary Formulations (F1-F5)

Effect of Tween-80 Concentration on Drug Release Profile

Effect of DMSO Concentration on Drug Release Profile]

Effect of Eucalyptus Oil Concentration on Drug Release Profile

Effect of Olive Oil Concentration on Drug Release Profile

Comparative Drug Release Profile of Optimized Formulations

In Vitro Permeation Profile of Optimized Formulations

5. DISCUSSION

The present study was focused on the development of transdermal matrix patches of metformin hydrochloride to overcome the limitations associated with oral delivery, such as short biological half-life, moderate bioavailability, and frequent dosing requirements. Transdermal drug delivery offers advantages including avoidance of first-pass metabolism, sustained plasma drug levels, and improved patient compliance (1,2).

Preformulation studies confirmed the identity and purity of metformin hydrochloride, as evidenced by melting point and FT-IR analysis consistent with reported standards (3). Compatibility studies indicated no significant interaction between the drug and excipients,

demonstrating the suitability of ethylcellulose (EC) and polyvinylpyrrolidone (PVP) for formulation development. Solubility studies revealed the necessity of a co-solvent system, and 20% methanol in PBS (pH 7.4) was selected to maintain sink conditions, in agreement with previous findings (4).

Matrix-type patches prepared using EC and PVP demonstrated that polymer composition plays a crucial role in controlling drug release. EC, being hydrophobic, retarded drug release, while PVP enhanced release due to its hydrophilic and pore-forming properties. Among the formulations, F3 (EC:PVP 3:2) showed optimal physicochemical properties and sustained drug release, indicating an appropriate balance between matrix integrity and drug diffusion (5).

The incorporation of permeation enhancers significantly improved drug release and permeation profiles. Tween-80 (2%) exhibited the highest enhancement in drug release and flux, likely due to its surfactant properties that improve wettability and reduce interfacial tension (6). Olive oil also demonstrated comparable enhancement, which can be attributed to the presence of oleic acid that disrupts lipid packing in the stratum corneum and enhances permeation (7). DMSO showed moderate enhancement due to its lipid-extracting and protein-denaturing effects, while eucalyptus oil exhibited comparatively lower enhancement, possibly due to limited interaction with the polymer matrix (8).

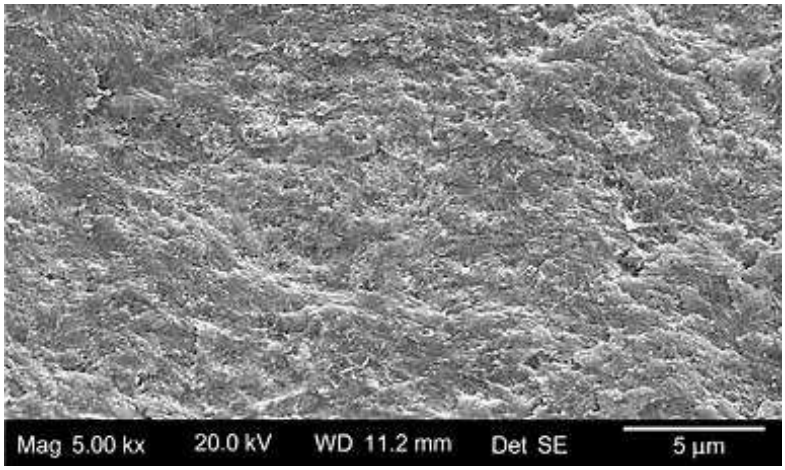
Drug release kinetics followed the Higuchi model with high correlation coefficients, indicating diffusion-controlled release. The Korsmeyer–Peppas model suggested non-Fickian (anomalous) transport, implying that both diffusion and polymer relaxation contributed to drug release (9). Similar release behavior has been reported for matrix-type transdermal systems (10).

Ex vivo permeation studies using rat skin demonstrated enhanced permeation with the use of permeation enhancers, with FT1 (2% Tween-80) showing the highest flux and lowest lag time. The correlation between in vitro and ex vivo results supports the reliability of the developed system (11).

Stability studies conducted under accelerated conditions showed that the optimized formulation remained stable with minimal drug degradation, confirming its suitability for storage and practical application (12).

The developed transdermal patch (FT1) demonstrated significant advantages, including sustained drug delivery over 24 hours, improved bioavailability, reduced dosing frequency, and minimized side effects. These findings indicate that transdermal delivery of metformin hydrochloride represents a promising alternative to conventional oral therapy for the management of diabetes mellitus.

Photograph of Optimized Transdermal Patch (FT1)



SEM Image of Optimized Transdermal Patch (FT1)

6. CONCLUSION

The present study was undertaken to develop and evaluate a transdermal matrix patch of metformin hydrochloride and assess its feasibility for transdermal drug delivery. Metformin hydrochloride, an oral hypoglycemic agent widely used in the management of diabetes mellitus, is associated with limitations such as moderate bioavailability, short half-life, and frequent dosing, which may reduce patient compliance and increase the risk of side effects.

The formulated transdermal patches exhibited satisfactory physicochemical characteristics, including uniform thickness, acceptable weight variation, high drug content, adequate

mechanical strength, and stability. Among all formulations, FT1 (containing EC:PVP in a 3:2 ratio, 20% w/w drug, 30% w/w dibutyl phthalate, and 2% w/w Tween-80) was identified as the optimized formulation based on superior in vitro drug release, enhanced permeation, and favorable physicochemical properties.

The optimized formulation demonstrated sustained drug release over 24 hours, improved permeation characteristics, and stability under accelerated conditions. The incorporation of Tween-80 significantly enhanced drug flux across the skin by modifying the stratum corneum barrier.

Overall, the findings of this study suggest that transdermal delivery of metformin hydrochloride is a promising alternative to conventional oral therapy. The developed system has the potential to improve bioavailability, reduce dosing frequency, minimize side effects, and enhance patient compliance in the management of diabetes mellitus.

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