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Formulation and Evaluation of Transdermal Patches of Repaglinide and Metformin

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Abstract:

Transdermal drug delivery systems (TDDS) offer a non-invasive and patient-compliant approach for the sustained delivery of therapeutic agents into systemic circulation. In this study, transdermal patches containing Repaglinide and Metformin were formulated using the solvent casting method. Various ratios of natural polymer (guar gum) and synthetic polymers (HPMC K-100 and ethyl cellulose) were incorporated, along with diethyl tartrate as a plasticizer and dimethyl sulfoxide as a permeation enhancer. Ten formulations (F1–F10) were prepared and evaluated for their physicochemical characteristics, drug content uniformity, and in vitro release performance. All the prepared patches exhibited smooth, uniform surfaces and consistent weight (approximately 728–737 mg). They also showed acceptable moisture content between 3.3% and 6.4%, while surface pH values ranging from 5.1 to 6.4 were found to be compatible with skin, suggesting low irritation potential. Drug content analysis demonstrated uniform drug distribution within the patches, with Repaglinide content ranging from 91.6% to 98.9% and Metformin from 92.4% to 99.1%, complying with pharmacopeial requirements. In vitro dissolution studies indicated that the polymer composition had a significant impact on drug release behavior. Formulations with an optimal balance of hydrophilic and hydrophobic polymers provided a more controlled and sustained release profile. Among all formulations, F8 showed the best performance, releasing 89.03% of Repaglinide and 96.01% of Metformin over a 24-hour period. The release kinetics followed a zero-order model with a non-Fickian diffusion mechanism. In conclusion, the developed dual-drug transdermal patches demonstrate potential for enhancing drug bioavailability, reducing dosing frequency, and improving therapeutic outcomes in the treatment of type 2 diabetes mellitus. Nevertheless, further in vivo studies are required to validate their clinical applicability and efficacy.

Keywords: Transdermal patches, drug delivery system, skin permeability, penetration enhancers, sustained release, microneedles, pharmaceutical innovation.

Introduction

Transdermal Drug Delivery Systems (TDDS) are an advanced drug administration approach in which medications are delivered across the skin into systemic circulation. This technique offers several advantages over conventional oral and parenteral routes, including avoidance of hepatic first-pass metabolism, reduced dosing frequency, and improved patient adherence. A major benefit of TDDS is its capability to provide sustained and controlled drug release, which helps maintain consistent plasma drug levels, reduces fluctuations, and minimizes adverse effects while improving therapeutic efficiency.[1-3]

A transdermal patch is a specialized adhesive dosage form designed to deliver a predetermined amount of drug through the skin over an extended period. In such systems, the drug may be incorporated either within a reservoir behind a semi-permeable membrane or dispersed in the adhesive matrix itself, from where it diffuses gradually, often assisted by body temperature. This delivery system offers clear advantages compared to oral, injectable, or topical routes; however, its effectiveness is limited by the skin's natural barrier function. The stratum corneum restricts permeation, allowing primarily small, lipophilic, and potent molecules to pass through effectively.[4-6]

The first successful commercialization of TDDS occurred in 1979 with FDA approval of scopolamine patches for motion sickness. Since then, TDDS has become a widely accepted non-invasive system for systemic drug delivery.

When applied to intact, clean skin, the drug permeates through the stratum corneum and subsequently diffuses across the epidermis and dermis, eventually reaching systemic circulation via the dermal microvasculature. Due to the large surface area of the skin and multiple potential application sites, TDDS offers considerable flexibility and ease of use. [7-8]

Pharmacokinetically, transdermal delivery provides more consistent drug plasma levels with reduced peak–trough variations, thereby lowering the risk of dose-related side effects. This system is especially beneficial for patients who have difficulty swallowing, experience nausea, or require simplified dosing regimens, as it supports self-administration and reduces dosing frequency.

Overall, transdermal delivery enhances bioavailability by bypassing first-pass metabolism and contributes to improved patient compliance and therapeutic outcomes. [9]

Materials

Repaglinide and Metformin were obtained as gift samples. Hydroxypropyl methylcellulose (HPMC K-100), guar gum, and ethyl cellulose served as polymers. Diethyl tartarate and dimethyl sulfoxide were used as plasticizer and permeation enhancer, respectively. All reagents and solvents used were of analytical grade.

Instrumentation

An analytical balance, digital pH meter, hot air oven, UV–Visible spectrophotometer, FTIR spectrophotometer, and HPLC system were employed during the study.

Preformulation Studies

Physicochemical characterization included descriptive tests, solubility analysis in various media, melting point determination (capillary method). Drug–excipient compatibility was assessed via FTIR spectroscopy over 4000–400 cm^{-1}.

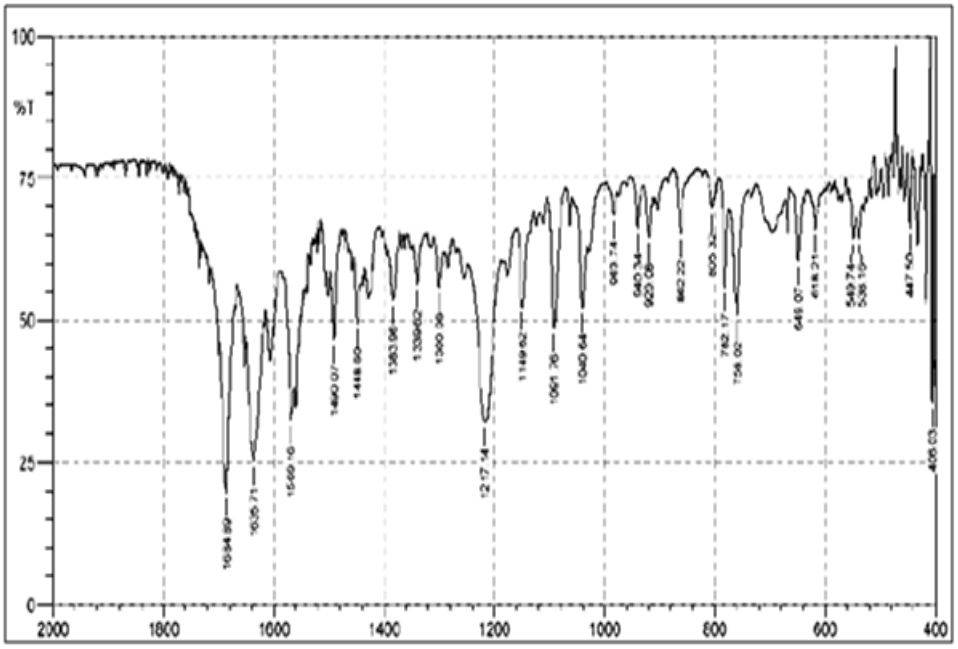

Figure 1: IR Spectrum of Repaglinide

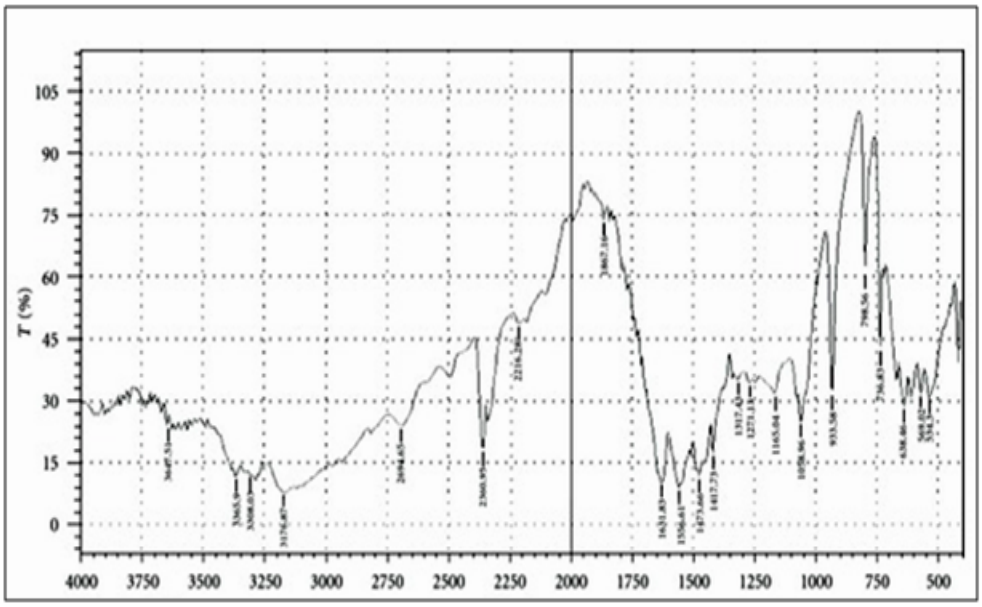

Figure 2: IR Spectrum of Metformin

Formulation of Transdermal Patches

Patches were prepared by the solvent casting method. Polymers were dissolved in a 1:1 chloroform–methanol mixture, followed by incorporation of drug, plasticizer, and permeation enhancer. The mixture was degassed, poured into circular glass moulds over a mercury surface, and dried at ambient conditions for 24 h, followed by oven drying (40–45 °C, 30 min). Dried patches (diameter 4.4 cm; surface area 15.21 cm²) were wrapped in aluminium foil and stored in a desiccator. Ten formulations (F1–F10) were prepared varying polymer composition.

Table 1: Formulation Batches

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Repaglinide	2	2	2	2	2	2	2	2	2	2
2.	Metformin	500	500	500	500	500	500	500	500	500	500
3.	HPMC K-100	12	18	24	--	--	12	18	24	--	--
4.	Guar Gum	--	--	60	90	120	--	--	60	90	120
5.	Ethylcellulose	--	120	180	--	240	--	--	120	180	240
6.	Diethyl tartarate	48	48	48	48	48	48	48	48	48	48
7.	Dimethyl sulfoxide	38	38	38	38	38	38	38	38	38	38
8.	Total Weight (mg)	700	700	700	700	700	700	700	700	700	700

Formulation Development

Ten batches (F1–F10) of Repaglinide and Metformin-loaded patches were prepared using the solvent casting method, incorporating varying ratios of natural (agar, guar gum) and synthetic polymers (HPMC, Eudragit RS, ethyl cellulose) to study the influence of polymer composition on physicomechanical and release properties. Glycerin was used as a plasticizer to enhance flexibility.

Evaluation of Patches

Patches were evaluated for thickness (micrometer screw gauge), weight uniformity, swelling index, moisture content, tensile strength, folding endurance, surface pH, and drug content uniformity. In-vitro drug release was studied using the USP paddle-over-disc method in phosphate buffer pH 7.4 at 37 ± 0.5 °C, 50 rpm, for 24 h. Aliquots were withdrawn at predetermined intervals, replaced with fresh medium, and analyzed spectrophotometrically.

Physicochemical Evaluation

All formulations exhibited uniform appearance, smooth surfaces, and flexibility without cracks. Thickness and weight variation were minimal, indicating reproducible casting. Moisture content ranged within acceptable limits, ensuring stability without risk of brittleness or microbial growth. Folding endurance values were satisfactory for all patches, with F5, F6, F8, and F10 demonstrating superior mechanical strength and flexibility due to optimized synthetic polymer content.

Surface pH values (6.2–6.9) were close to skin pH, minimizing the risk of irritation.

Table 2: Evaluation of Patches

Formulation	Weight (mg)	Moisture Content	Swelling Index (% at 30 min)	Tensile Strength (kg/mm^2)	Folding Endurance	Drug Content Repaglinide	Drug Content Metformin	Surface pH
F1	730.48	5.6 %	254.75 %	0.76	>300	95.5±0.02	98.8±0.47	5.8
F2	732.72	4.7 %	245.94 %	0.53	>200	96.6±0.06	96.6±0.84	6.4
F3	734.32	5.3 %	123.32 %	0.32	>300	98.3±0.09	99.1±0.02	5.1
F4	736.81	5.6 %	153.65 %	0.79	>300	93.2±0.05	94.8±0.03	5.6
F5	732.02	5.8 %	156.84 %	0.23	>400	96.1±0.06	92.4±0.26	6.1
F6	731.74	3.3 %	123.48 %	0.45	>200	95.4±0.03	97.6±0.09	5.7
F7	730.95	4.7 %	123.75 %	0.29	>200	97.8±0.11	93.2±0.07	5.4
F8	728.32	3.6 %	164.62 %	0.63	>200	98.9±0.22	98.3±0.08	5.2
F9	729.10	4.2 %	165.35 %	0.27	>200	93.5±0.27	92.4±0.16	4.6
F10	730.07	6.4 %	197.16 %	0.62	>300	91.6±0.08	96.6±0.23	5.3

Drug Content Uniformity

Drug content across all batches ranged from 94.95% to 102.32%, reflecting homogeneous drug dispersion within the polymer matrix. The slight variation observed was within pharmacopeial limits, ensuring dose uniformity.

In-vitro Drug Release: Release profiles indicated that polymer composition significantly influenced the release rate. Patches containing higher proportions of synthetic polymers exhibited more controlled release compared to those with predominantly natural polymers.

Formulations F5, F6, F8, and F10 sustained drug release over 24 hours, with F8 showing the highest cumulative release of 89.03%.

This enhanced performance was attributed to the balanced ratio of hydrophilic (HPMC) and hydrophobic (Eudragit RS, ethyl cellulose) polymers, which regulated drug diffusion and matrix erosion.

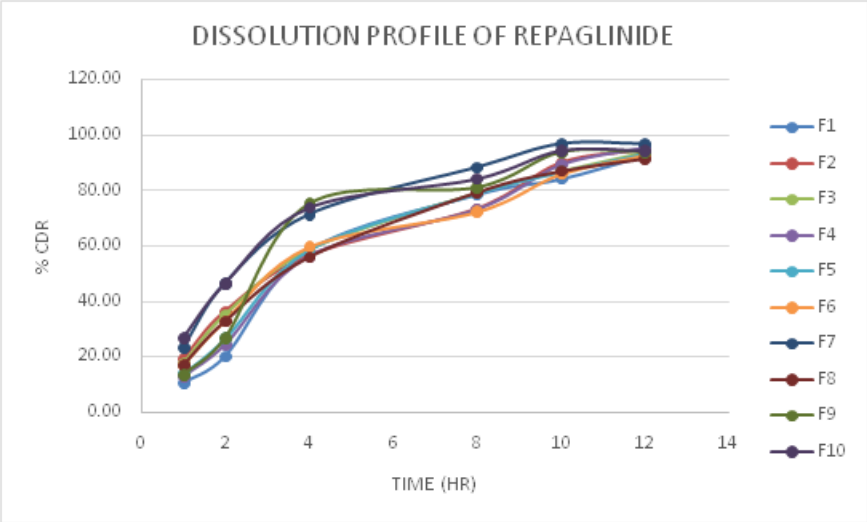

Figure 3: Dissolution Profile of Repaglinide

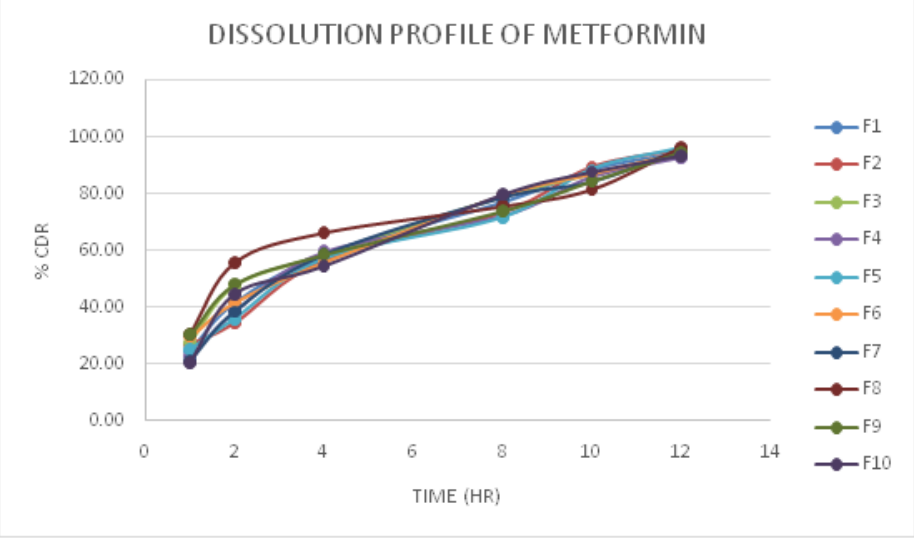

Figure 4: Dissolution Profile of Metformin

Conclusion

The present study successfully developed and evaluated transdermal patches of Repaglinide and Metformin using varying combinations of natural (guar gum) and synthetic polymers (HPMC K-100, ethyl cellulose) via the solvent casting method.

All formulations exhibited acceptable physicochemical characteristics, including uniform thickness, weight, moisture content, folding endurance, and surface pH close to skin pH, minimizing the risk of irritation.

Drug content uniformity remained within pharmacopeial limits, confirming homogeneous dispersion in the polymer matrix. In-vitro drug release studies revealed that polymer composition significantly influenced release kinetics. Formulations incorporating both hydrophilic and hydrophobic polymers achieved sustained drug release, with F8 demonstrating the most favorable profile — controlled release over 24 hours with a cumulative release of 89.03% for Repaglinide and 96.01% for Metformin. Kinetic modeling indicated predominantly zero-order release with non-Fickian diffusion, suggesting a combined mechanism of diffusion and polymer relaxation.

Overall, the optimized formulation (F8) shows potential as a patient-friendly, non-invasive alternative to conventional oral therapy for type 2 diabetes mellitus, with the advantages of prolonged drug release, improved bioavailability, and reduced dosing frequency. Further ex-vivo and in-vivo studies are warranted to validate its clinical efficacy and safety.

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