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QUANTITATIVE EVALUATION OF HPMC POLYMER CONCENTRATION AND ITS EFFECT ON DRUG FLUX AND RELEASE KINETICS IN TRANSDERMAL PATCHES USING CETIRIZINE HYDROCHLORIDE AS A MODEL DRUG

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ABSTRACT

Transdermal drug delivery systems (TDDS) represent an effective approach to conventional oral therapy by providing sustained drug release, bypassing hepatic first-pass metabolism, and improving patient compliance through non-invasive administration. However, achieving predictable drug release remains a major challenge in matrix-type transdermal systems, as drug flux is strongly influenced by polymer concentration. The present study investigates the role of polymer concentration in modulating drug flux and achieving controlled drug release in HPMC-based transdermal systems. Patches were formulated using hydroxypropyl methylcellulose (HPMC) at varying concentrations (1–5% w/w) to examine how polymer concentration regulates drug flux and drug release kinetics. Cetirizine hydrochloride was selected as the model drug due to its suitable physicochemical properties and its therapeutic relevance in allergic conditions where sustained antihistaminic activity may be beneficial. The prepared patches were evaluated through in vitro permeation studies to determine cumulative drug release and steady-state flux as indicators of drug transport across the transdermal system. The resulting release profiles were further analyzed using Higuchi and Korsmeyer–Peppas kinetic models to characterize the mechanism of drug release, while statistical comparison among the prepared patches was carried out using analysis of variance (ANOVA). Through the integration of flux determination, kinetic modeling, and statistical evaluation, this study seeks to establish a quantitative understanding of how polymer concentration can regulate drug transport in transdermal systems, supporting the development of controlled and predictable transdermal drug delivery systems.

KEYWORDS: Transdermal Drug Delivery Systems (TDDS); Hydroxypropyl Methylcellulose (HPMC); Cetirizine Hydrochloride; Higuchi Model; Korsmeyer–Peppas Model; ANOVA.

1. INTRODUCTION

In modern pharmaceutical science, transdermal patches are evolving as a better and safer approach to drug delivery, offering a needle-free alternative with the potential for controlled drug release.[1,2] However, despite these advantages, achieving consistent and reliable drug delivery remains a challenge.[2,3] Following this understanding, we started questioning whether the limitations observed in transdermal patches are truly due to the system itself or the way the formulation is designed. In many cases, we observe issues such as initial burst effect, dose dumping, and fluctuating permeation rate, which suggest that drug release is still influenced more by external physiological conditions than by the formulation.[3,12,13] This led us to focus on the idea that effective control should exist within the system itself rather than relying on biological heterogeneity. Based on this, the present study is designed on the hypothesis that by varying polymer concentration within the range of 1–5%, we can control the drug release

behavior and release kinetics, thereby achieving a more sustained and uniform flow of drug from transdermal patches.[8,9] In this context, hydroxypropyl methylcellulose (HPMC) was selected as the polymer due to its ability to form a uniform, continuous film and its influence on drug diffusion.[5,8] Cetirizine hydrochloride was selected as the model drug due to its need for maintaining steady plasma levels in allergic conditions, where fluctuations reduce drug efficacy, and its suitable physicochemical properties underpin its use in transdermal delivery systems.[6,7,17] The study focuses on understanding the relationship between polymer concentration and drug transport parameters, including cumulative drug release, transdermal flux, and release kinetics. In-vitro drug release studies were performed, followed by kinetic modeling using established models such as Higuchi model and Korsmeyer–Peppas model,[10,11] along with statistical validation using ANOVA. Through this systematic approach, the study aims to establish a quantitative correlation between polymer concentration and controlled drug delivery, ultimately providing a formulation-based strategy to achieve more predictable and sustained drug release.[15,16]

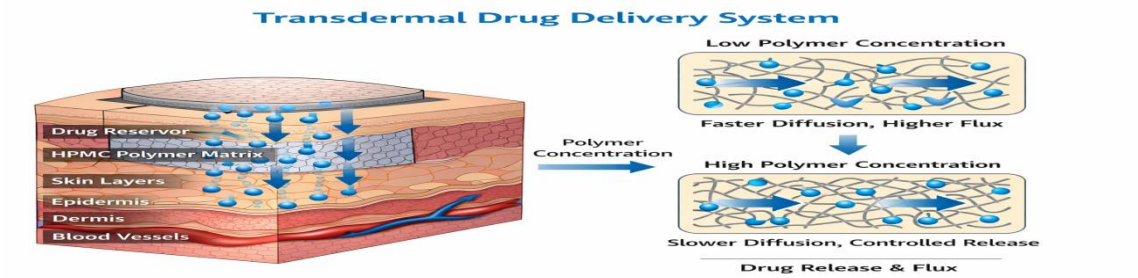

Figure 1: Schematic illustration of matrix-type transdermal drug delivery system depicting the influence of polymer concentration on drug diffusion and flux.

2. MATERIALS AND METHODS

2.1 Materials

Cetirizine hydrochloride was used as the model drug. Hydroxypropyl methylcellulose (HPMC) was used as the polymer. Polyethylene glycol 400 (PEG-400) was used as a plasticizer. Ethanol and distilled water were used as solvents. All the materials used were of analytical grade and procured from Labmate, Ranchi.

2.2 Preparation Of Matrix Type Transdermal Patches

Transdermal patches were prepared using a solvent casting technique. Prior to formulation, all glassware was sterilized in a hot air oven. HPMC was accurately weighed in different concentrations (1–5% w/w) and dispersed in distilled water under continuous stirring using a magnetic stirrer to obtain a uniform polymeric solution. PEG-400 was then used as a plasticizer into each formulation and mixed thoroughly. Cetirizine hydrochloride was finely powdered and added to the polymeric solution with constant stirring to ensure uniform distribution. Ethanol was introduced to improve the homogeneity of the mixture. The resulting solution was poured into petri plates and allowed to dry at room temperature for 24 hours to facilitate solvent evaporation. After drying, the films were removed, cut into patches of uniform size, and stored in a desiccator for further studies.

2.3 Formulation Design

Different formulations of transdermal patches were prepared by varying the concentration of HPMC while keeping the drug and other components constant. The composition of different formulations is given in Table 1.

Table 1: Composition of Transdermal Patch Formulations.

Formulation	Cetirizine HCl (mg)	HPMC (% w/w)	PEG-400 (mL)	Ethanol (mL)	Distilled Water (mL)
F1	10	1	2	5	10
F2	10	2	2	5	10
F3	10	3	2	5	10
F4	10	4	2	5	10

Note: HPMC concentration was varied in different formulations, whereas the drug, plasticizer (PEG-400), and solvent were maintained constant.

2.4 Evaluation Of Transdermal Patches

2.4.1 Thickness

The thickness of the prepared transdermal patches was measured using a digital micrometer at different points, and the average value was recorded.

2.4.2 Weight Variation

Individual patches were weighed using an analytical balance and uniformity was noted.

2.4.3 Folding Endurance

Folding endurance of the patches was determined by repeatedly folding the patch at the same place until it broken up. The number of folds required to break the patch was then noted.

2.4.4 Drug Content

A patch was cut into pieces and dissolved in a mixture of ethanol and phosphate buffer (pH 7.4) and filtered. The solution was scanned over a suitable wavelength range using a UV–Visible spectrophotometer to determine the λmax of cetirizine hydrochloride. The drug content was then quantified at 231 nm.

2.4.5 In-vitro Drug Release Study

In-vitro drug release was performed using a Franz diffusion cell with an egg membrane as the diffusion barrier between donor and receptor compartments.[18] The patch was placed on the membrane, and the receptor compartment contained phosphate buffer (pH 7.4) maintained at 37 ± 0.5°C under continuous stirring. Samples were withdrawn at intervals based on the half-life of cetirizine hydrochloride and analyzed using UV–Visible spectrophotometry.

2.4.6 Determination of Drug Flux

The steady-state drug flux (Jss) was determined from the slope of the linear portion of the cumulative drug release versus time plot (Jss = dQ/dt), where Q represents the cumulative amount of drug permeated and t represents time.

2.5 Drug Release Kinetics

In-vitro drug release data were analyzed using Higuchi and Korsmeyer–Peppas models.[10,11] The data were fitted using Microsoft Excel and GraphPad Prism by plotting cumulative drug release against the square root of time (Higuchi) and log cumulative drug release against log time (Korsmeyer–Peppas). Linear regression was applied, and R^2 values were used to identify the best fitting model. The release exponent (n) was obtained from the slope of the Korsmeyer–Peppas plot.

2.6 Statistical Analysis

Statistical analysis was performed using two-way ANOVA in GraphPad Prism to assess differences among formulations, with $p < 0.05$ taken as the level of significance.

3. RESULTS AND DISCUSSION

The developed cetirizine hydrochloride transdermal patches exhibited consistent physicochemical characteristics with noticeable variation across formulations. Thickness increased from 0.23 ± 0.01 mm in F1 to 0.34 ± 0.02 mm in F4, while weight increased from 110.2 ± 1.5 mg to 136.8 ± 2.4 mg, confirming progressive matrix build-up with increasing HPMC concentration. Folding endurance also improved from 185 ± 4 to 228 ± 7, indicating adequate flexibility and mechanical strength. Drug content remained within acceptable limits across all formulations, ranging from 97.4 ± 0.8% to 99.0 ± 0.5%, indicating uniform drug distribution in the polymer matrix. This shows that as HPMC concentration increases, the matrix becomes denser.[5,8] Drug release decreased as HPMC concentration increased across all formulations. Formulation F1 exhibited the highest cumulative drug release, reaching 86 ± 0.5% at 24 h, whereas F4 showed the lowest release at 64 ± 0.5%. The release profile followed the order F1 > F2 > F3 > F4, showing that higher polymer concentration slowed drug diffusion and resulted in a more controlled pattern of drug release.. The cumulative amount of drug released also decreased with increasing polymer concentration, with F1 showing the highest values throughout the study period and F4 the lowest. This shows that at higher HPMC concentrations, the matrix becomes more compact, which restricts drug movement and slows down drug release.[8] Flux data followed the same pattern. Steady-state flux decreased from 697.39 ± 8.5 µg/cm²/hr for F1 to 436.52 ± 7.0 µg/cm²/hr for F4, showing that higher HPMC concentrations reduced drug permeation across the membrane. This is a strong indication that polymer concentration directly controls drug transport by increasing matrix density and reducing diffusion.[4,8] The flux trend is therefore fully aligned with the release profile and supports the formulation hypothesis Kinetic analysis supported the release mechanism. The Higuchi model gave high correlation coefficients for all formulations, from $R^2 = 0.9651$ for F1 to $R^2 = 0.9834$ for F4, pointing diffusion-controlled release from a matrix system. The slope values decreased from 18.70 to 13.85 as polymer concentration increased, indicating slower drug diffusion at higher HPMC concentrations. Korsmeyer–Peppas analysis yielded n values between 0.6222 and 0.7454, demonstrating anomalous transport behavior. This means the release mechanism was governed by a combination of diffusion and polymer relaxation/swelling rather than pure Fickian diffusion.[11] Statistical analysis by two-way ANOVA confirmed that both time and formulation had a highly significant effect on drug release, with $p < 0.0001$ for both factors. Time explained 66.88% of the variation, while formulation accounted for 25.78%, showing that polymer concentration had a strong effect on release, although time remained the main factor. Overall, HPMC concentration played a key role in controlling both drug release and flux from the transdermal patches.

Table 2: Physicochemical Properties of Formulations (Mean ± SD, n = 3)

Formulation	Thickness (mm)	Weight (mg)	Folding Endurance	Drug Content (%)
F1	0.23 ± 0.01	110.2 ± 1.5	185 ± 4	97.4 ± 0.8
F2	0.26 ± 0.01	118.6 ± 1.8	198 ± 5	98.2 ± 0.6
F3	0.30 ± 0.02	127.4 ± 2.1	212 ± 6	99.0 ± 0.5
F4	0.34 ± 0.02	136.8 ± 2.4	228 ± 7	98.6 ± 0.7

Table 3: Cumulative % Drug Release of Cetirizine Hydrochloride Transdermal Patches (Mean ± SD, n = 3)

Time (h)	F1 (% Release ± SD)	F2 (% Release ± SD)	F3 (% Release ± SD)	F4 (% Release ± SD)
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1	12 ± 0.5	10 ± 0.4	8 ± 0.5	6 ± 0.6
2	23 ± 0.6	19 ± 0.5	16 ± 0.6	12 ± 0.7
4	41 ± 0.7	35 ± 0.6	29 ± 0.7	23 ± 0.8
8	62 ± 0.9	54 ± 0.8	46 ± 0.9	37 ± 1.0
24	86 ± 1.1	79 ± 1.0	72 ± 1.1	64 ± 1.2

Table 4: Cumulative Amount of Drug Released (Mean ± SD, n = 3)

Time (h)	F1 (µg ± SD)	F2 (µg ± SD)	F3 (µg ± SD)	F4 (µg ± SD)
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1	1200 ± 45	1000 ± 40	800 ± 45	600 ± 50
2	2300 ± 55	1900 ± 50	1600 ± 55	1200 ± 60
4	4100 ± 65	3500 ± 60	2900 ± 65	2300 ± 70
8	6200 ± 80	5400 ± 75	4600 ± 80	3700 ± 85

Table 5: Steady-State Flux of Formulations.

Formulation	Flux (µg/cm²/hr ± SD)
F1	697.39 ± 8.5
F2	617.39 ± 8.0
F3	531.30 ± 7.5
F4	436.52 ± 7.0

Table 6: Higuchi Kinetic Parameters.

Formulation	Slope (kH)	R^2	Equation
F1	18.70	0.9651	Y = 18.70X − 0.5159
F2	17.18	0.9740	Y = 17.18X − 1.939
F3	15.62	0.9816	Y = 15.62X − 3.111
F4	13.85	0.9834	Y = 13.85X − 4.352

Table 7: Korsmeyer–Peppas Kinetic Analysis Table.

Formulation	n Value	Mechanism	R^2
F1	0.6222	Anomalous transport	0.9467
F2	0.6550	Anomalous transport	0.9567
F3	0.6911	Anomalous transport	0.9649
F4	0.7454	Anomalous transport	0.9750

Table 8: ANOVA Results.

Source	% Variation	F value	P value	Significance
Time	66.88	36.46	<0.0001	Significant
Formulation	25.78	14.05	<0.0001	Significant

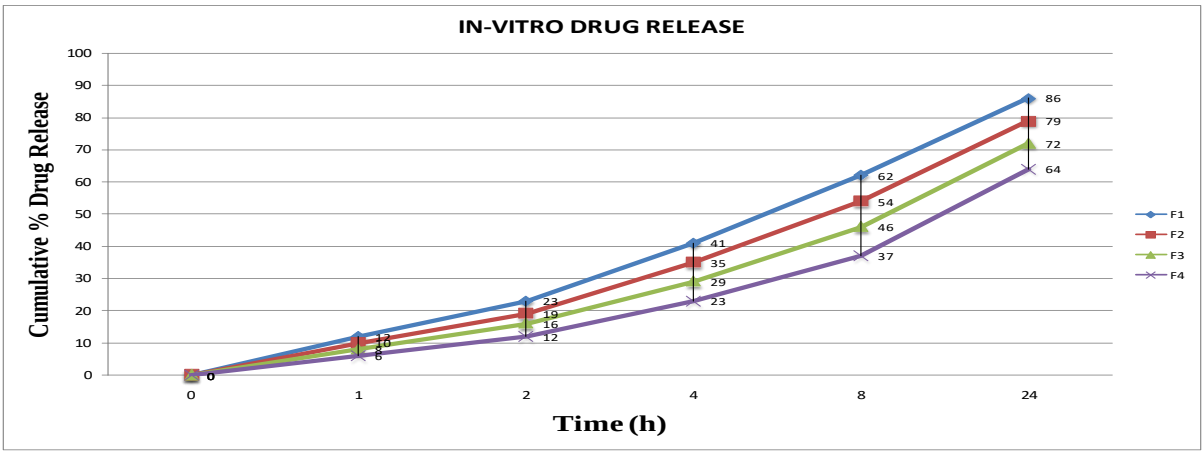

Figure 2: In-vitro Drug Release Profile of Transdermal Patches (Mean ± SD).

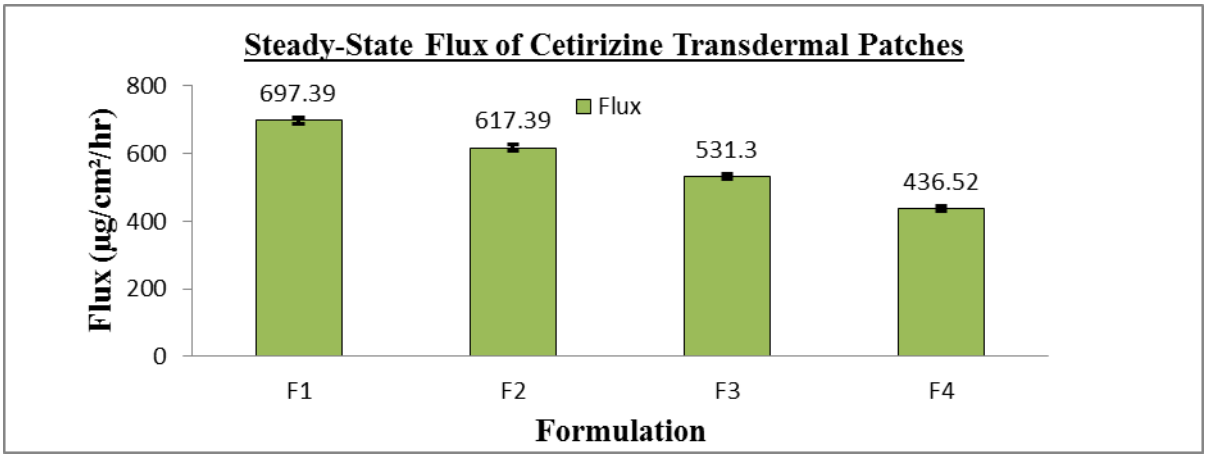

Figure 3: Flux vs Formulation Plot.

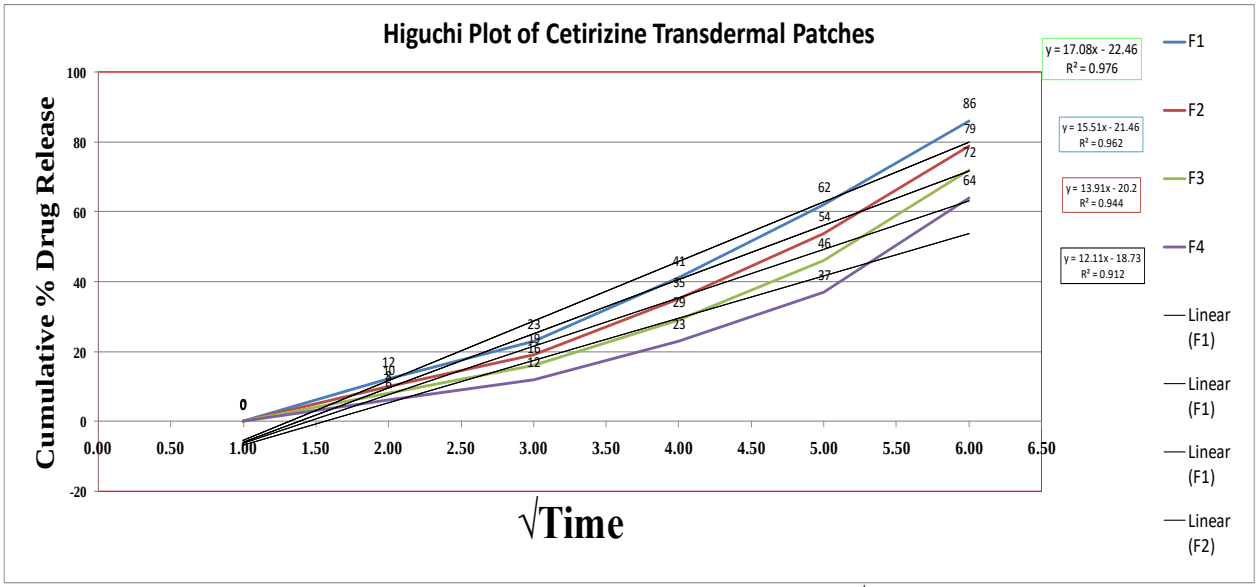

Figure 4: Higuchi Plot (Cumulative Release vs √Time).

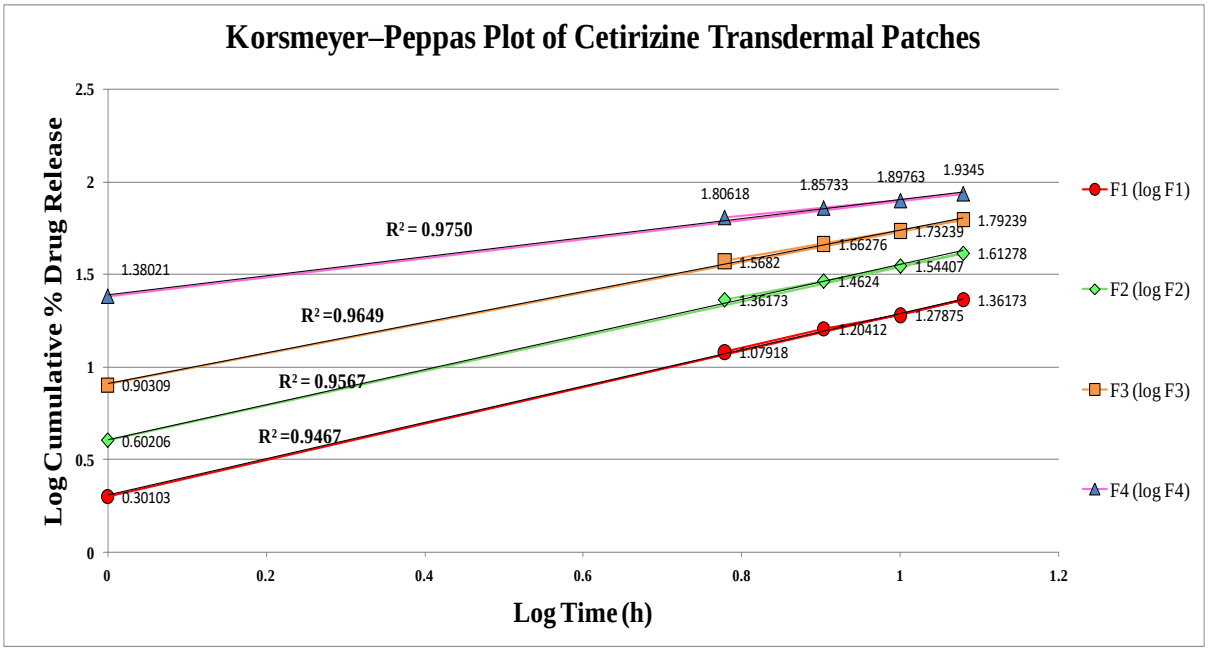

Figure 5: Korsmeyer–Peppas Plot (log-log).

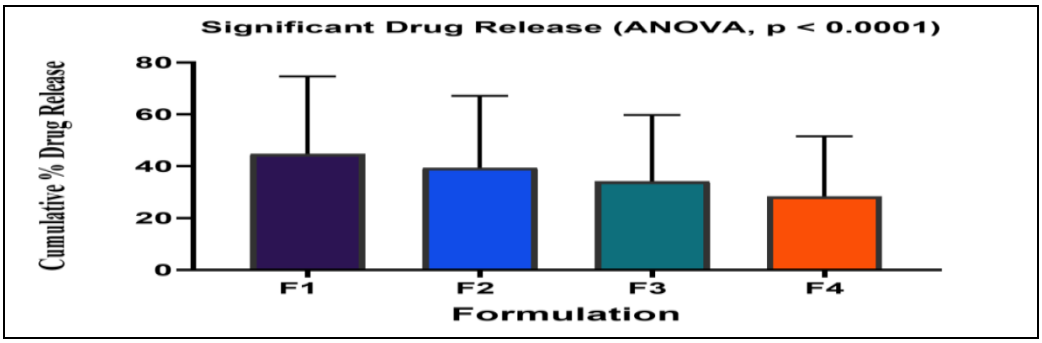

Figure 6: Effect of Time and Polymer Concentration on Cumulative Drug Release (Two-way ANOVA Analysis)

4. CONCLUSION

The results confirmed that increasing polymer concentration significantly reduced cumulative drug release and permeation flux, with formulation F1 exhibiting the highest release and flux, while F4 showed the most sustained release profile. This highlights the role of polymer concentration in controlling drug diffusion through the matrix. Kinetic analysis indicated that drug release followed the Higuchi model (R^2 > 0.96), suggesting diffusion-controlled release, while Korsmeyer–Peppas modeling revealed anomalous (non-Fickian) transport, suggesting the involvement of both diffusion and polymer relaxation mechanisms. Statistical analysis using two-way ANOVA demonstrated that both time and formulation had a highly significant effect on drug release ($p < 0.0001$), confirming the influence of polymer concentration on release behavior**.** Overall, the results show that polymer concentration had a major effect on drug release and flux, stating that by changing the polymer concentration, we can achieve controlled and sustained transdermal drug delivery.

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