RESEARCH ARTICLE

Optimizing Transdermal Patch Design: A Quality by Design Approach for Dysmenorrhea Relief

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ABSTRACT

This study explores the potential of transdermal patches as a systemic delivery system for donepezil (DPZ), aiming to circumvent hepatic first-pass metabolism and mitigate oral administration-associated side effects. DPZ, known for its poor solubility and adverse effects, is formulated into transdermal patches using a matrix-type approach with PVP K30 and HPMC K100 polymers alongside dimethyl sulfoxide as a plasticizer. Through solvent casting on a mercury surface, the patches are prepared and assessed for physical properties and drug-excipient interactions using FTIR analysis. The results demonstrate satisfactory physical characteristics, including appearance, weight variation, and tensile strength. Notably, formulations containing HPMC K100 (400 mg) and PVP K30 (300 mg) exhibit enhanced DPZ discharge, signifying their potential as an effective drug delivery system for mitigating DPZ-associated side effects.

Keywords: Donepezil, Delivery, Patch, Permeation, Discharge.

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INTRODUCTION

Transdermal systems signify an advanced slant for administering medications by the skin, offering many merits over traditional oral or parenteral routes. These systems utilize patches, gels, creams, or other formulations to bring drugs across the skin barrier and into the systemic circulation.[1] One of the primary benefits of transdermal delivery is the avoidance of first-pass metabolism in the liver, which can significantly affect drug bioavailability.[2] By bypassing this metabolic pathway, transdermal delivery can enhance drug absorption and efficacy while reducing the risk of gastrointestinal irritation or degradation. Moreover, transdermal drug delivery provides a controlled discharge of medications, allowing for sustained plasma concentrations over an extended period. This controlled discharge profile can lead to better actions, reduced dosing frequency, and enhanced patient acceptance. Transdermal drug delivery systems (TDDS), consist of a backing layer, drug reservoir or matrix, adhesive layer, and discharge liner.[3] These patches adhere to the skin and gradually discharge the medication into the bloodstream, maintaining steady plasma levels.[4]

Donepezil, an acetylcholinesterase inhibitor, is primarily used in Alzheimer's disease treatment, a progressive disorder marked by reasoning decline and memory loss. By elevating brain acetylcholine levels, donepezil mitigates symptoms related to acetylcholine deficiency resulting from neuronal degeneration in Alzheimer's. Typically administered orally once daily, donepezil's dosage is gradually adjusted to optimize therapeutic effects while minimizing adverse reactions, such as nausea and diarrhea. Although it doesn't cure Alzheimer's or halt its progression, donepezil improves rational function and quality of life, delaying severe symptom onset. Side effects like nausea, diarrhea, and insomnia are common, while severe reactions like bradycardia and hallucinations can occur, especially in elderly or cardiovascularly compromised patients. Despite its limitations, donepezil remains a pivotal therapy in Alzheimer's management, offering symptomatic relief and enhancing overall functioning. Ongoing research aims to further understand its benefits and explore novel treatment avenues for Alzheimer's disease. The Quality by Design (QbD) approach, incorporating Design of Experiments (DoE), revolutionizes pharmaceutical development by systematically optimizing processes to ensure product quality and efficacy. Unlike the traditional trial-and-error method, QbD integrates scientific principles and statistical tools to understand and control product variability, enhancing

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manufacturing robustness and regulatory compliance. QbD's primary advantage lies in its proactive and systematic approach to process development, focusing on critical quality attributes (CQAs) and their relationship to critical process parameters (CPPs). By employing DoE, QbD identifies the CPPs that significantly impact CQAs, enabling precise control over manufacturing variables to achieve desired product performance consistently. Furthermore, QbD reduces development time and cost by streamlining experimentation and analysis. DoE allows for the exploration of multiple factors and their interactions simultaneously, maximizing information yield with minimal experimental runs. This holistic approach accelerates process optimization, expediting product launch and market entry. Additionally, QbD promotes a deeper understanding of product performance and behavior throughout its lifecycle. By elucidating the cause-and-effect relationships between process parameters and product attributes, QbD facilitates risk mitigation and continuous improvement, ensuring product quality and patient safety.

The work aims to make several *in-vitro* studies that have assessed transdermal patches for controlled discharge, highlighting donepezil (DPZ) as a promising candidate for such formulations. Experimental evidence suggests that DPZ is well-suited for transdermal patches designed to provide controlled discharge. These patches typically incorporate a matrix polymer blend of hydroxypropyl methylcellulose (HPMC) K100, which effectively regulates the discharge of DPZ. The use of HPMC K100 in combination with other polymers ensures precise control over the discharge kinetics of DPZ and presents latent advantages in terms of activity and acceptance.

MATERIAL AND METHODS

Materials

Glenmark Pharmaceuticals, Vadodara, generously supplied donepezil, while HPMC K100 dimethyl sulfoxide (DMSO) and PVP K30 were obtained from Qualigens, India. The cellulose acetate membrane was sourced from Chemtech International, India. All chemicals and materials were of AR grade.

Methods

A solvent casting method was adopted. HPMC K100 and HPMC K100 were dissolved in selected ratios in ethanol and dichloromethane (DCM) at a ratio of 2:1. After adding DMSO, the mixture was stirred for 30 minutes. DPZ was then combined into the polymeric solution with stirring. The resulting polymeric solutions of DPZ were placed in a petri dish and air-dried. Subsequently, the dried transdermal drug delivery patches (DTDP) were cut into squares measuring 1x1 cm^2. These DTDPs were packed in aluminum foil and stored in desiccators for further analysis. Nine combinations of two factors were compared using the central composite design (Table 1). Design Expert Software (Version 11) was employed to analyze folding endurance (FE) and drying resistance (DR@24h). The equations between independent variables (HPMC K100 and HPMC K100) and responses (FE and DR@24h) were derived by subjecting the results to statistical evaluation. Stepwise forward and backward elimination were utilized to assess the significant factors in the regression analysis. In the full model, factors with a non-significant ($p > 0.05$) effect on the dependent variables were disregarded as they had an insignificant impact.[5]

Table 1: Various formulae of patches

Formulation	*Donepezil (mg)*	*HPMC K100(mg)*	*PVP K30 (mg)*	*Dichloromethane (ml)*	*DMSO (mL)*
DTDP-1	50	400	300	20	1.5
DTDP-2	50	500	300	20	1.5
DTDP-3	50	400	400	20	1.5
DTDP-4	50	500	400	20	1.5
DTDP-5	50	379.3	350	20	1.5
DTDP-6	50	520.7	350	20	1.5
DTDP-7	50	450	279.3	20	1.5
DTDP-8	50	450	420.7	20	1.5
DTDP-9	50	450	350	20	1.5

Evaluations

Compatibility studies

In the process of analyzing the FTIR spectrum for donepezil (DPZ), a common technique was employed. Initially, DPZ was blended with potassium bromide (KBr) to create a homogeneous mixture. This mixture was then further processed through trituration, a method involving grinding and mixing to form pellets. These pellets, containing a representative sample of DPZ and KBr, were then subjected to spectroscopic measurements. This procedure allowed for the acquisition of the infrared spectrum of DPZ. FTIR spectroscopy, a powerful analytical tool, operates on the principle that molecules absorb infrared radiation at characteristic frequencies, providing information about their chemical structure and composition. By examining the interactions between DPZ and infrared radiation, valuable insights into its molecular properties and functional groups can be obtained, aiding in its characterization and identification.[6]

Physical appearance

Visual inspection was done to assess the color, clarity, elasticity, and levelness of all donepezil transdermal drug patches (DTDPs). Furthermore, the thickness of the DTDPs was measured using a micrometer (H. L. Scientific Industries, Ambala Cantt, India) in triplicate, and the average was assessed to ensure accuracy and consistency in the measurements. This comprehensive evaluation aimed to ascertain the physical characteristics and quality attributes of the DTDPs, providing valuable information regarding their suitability for transdermal drug delivery applications.[7, 8]

Uniformity of weight

Three randomly selected DTDPs from each batch were individually weighed, and the average weight of five DTDPs was determined. This process ensured accurate measurement and provided representative data regarding the weight characteristics of the DTDPs across different batches, contributing to the overall assessment of their quality and consistency.[9, 10]

Folding Endurance

In this experiment, a single DTDP was subjected to repeat folding at the same spot until it reached the point of breakage. This method, known as FE testing, assesses the mechanical strength and durability of the film. The number of times the DTDP could be folded in the same location without experiencing any interruption or failure was recorded. This measurement provides valuable information about the flexibility and resilience of the DTDP, which are crucial factors in determining its suitability for practical application and handling during use.[11,12]

Tensile strength

To provide support for the DTDP during testing, an adhesive tape was affixed to one end of the DTDP, while a small pin was inserted into the adhesive tape on the opposite end to maintain its alignment as it stretched. The adhesive tape was punctured where the pin was inserted to secure it firmly. A thread was attached to the pin, passed over a pulley, and connected to a weight at the other end to exert tension on the DTDP. A small pointer moved along the thread as the tension increased, recording the force exerted on the DTDP on a graph paper baseplate. Gradually, additional weights were included in the pan to accelerate the hauling force until the DTDP broke, measuring the breaking force required to rupture the DTDP. This method allowed for the precise determination of the tensile strength of the DTDP under controlled conditions.[13,14]

Moisture content

The Donepezil Transdermal Drug Patches (DTDP) are stored at room temperature in desiccators containing calcium chloride (CaCl2) to maintain a dry environment. At specified intervals, the DTDPs are removed and weighed until their weight stabilizes. The moisture content of the DTDP is judged using the following formula:[15,16]

$$\text{Moisture content} \ \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} X100$$

Assay

The DTDP was cut into 1 cm^2 squares, and each square was placed in a tube containing 100 mL of PBS. The medium was then stirred using a magnetic bead to ensure uniform dispersion of the DTDP contents. Subsequently, the contents of the tube were filtered using Whatman filter paper, and spectrophotometric analysis was conducted at a wavelength of 271 nm to assess the level of the drug discharged from the DTDP. This process was repeated until consistent results were obtained, ensuring accuracy and reliability in the analysis.[17,18]

In-vitro Diffusion Study

In the *in-vitro* diffusion studies, Franz diffusion cell receptors with a capacity of 22 mL were utilized. The receiver section of each cell was filled with 22 mL of PBS at pH 7.4. The DTDP samples were firmly placed onto the center of the cellophane membrane, securing them to the donor compartment. The assembly was arranged so that the membrane just made contact with the surface of the recipient compartment. Maintaining a constant temperature of 32°C was ensured using a water bath throughout the experiment.[19] At regular intervals of 12 hours, samples were withdrawn from the receptor cells and analyzed for the presence of the drug. Equal volumes of PBS were added to each receptor cell after each sampling interval to maintain sink conditions. This rigorous protocol ensured accurate and consistent measurement of drug diffusion from the DTDP.[20]

RESULTS AND DISCUSSION

The FTIR analysis conducted in this study aimed to elucidate the chemical and physical connections between the excipients and DPZ. Figure 1 illustrates the IR spectrum obtained from the analysis. Upon examination of the IR spectrum of the mixture containing DPZ and the polymers, it was observed that the main peaks remained unchanged. This lack of alteration in the main peaks suggests the absence of any significant physical interface between DPZ and the polymers, namely HPMC K100 and PVP K30. This finding indicates that DPZ exists in its molecular form without undergoing any substantial chemical modifications or connections with the excipients. Consequently, the formulation of DTDP incorporating DPZ and the selected polymers is unlikely to induce any adverse chemical reactions or alterations in the molecular structure of DPZ. Thus, the FTIR analysis provides valuable insights into the compatibility of DPZ with the selected excipients, supporting their suitability for formulating DTDP for effective drug delivery.[21]

The DTDP exhibited desirable physical and chemical characteristics, as illustrated in Figure 2. These properties include satisfactory appearance, uniform thickness, uniformity

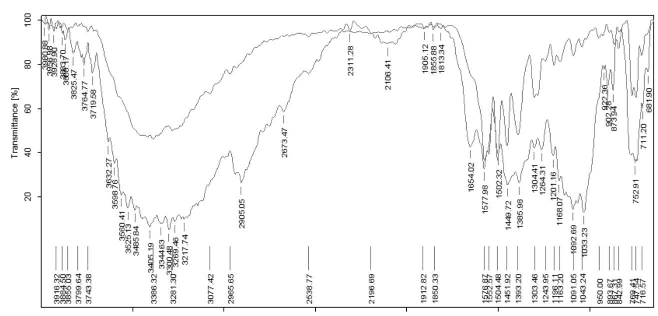

Figure 1: FTIR spectra of DPZ and its excipients

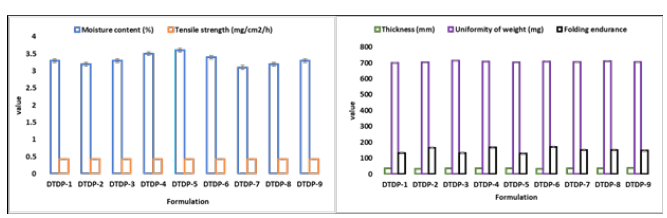

Figure 2: Graphical depiction of the physicochemical assets of DTDP

in weight and content, FE, tensile strength, moisture content, elongation at break, and % drug content. Notably, DTDP-1, DTDP-5, and DTDP-8 demonstrated the highest drying resistance at 24 hours (DR@24h), suggesting their superior ability to maintain integrity and drug discharge over time. Additionally, these batches exhibited optimal folding performance, particularly DTDP-9. The tensile strength of all batches ranged from 0.421 ± 0.02 to 0.429 ± 0.01, indicating robust mechanical properties. Furthermore, the moisture content of all batches fell within acceptable limits, ensuring stability and suitability for transdermal drug delivery applications. Overall, these findings affirm the successful formulation of DTDP with favorable physical and chemical attributes, highlighting their potential for effective and reliable drug delivery.[22-26]

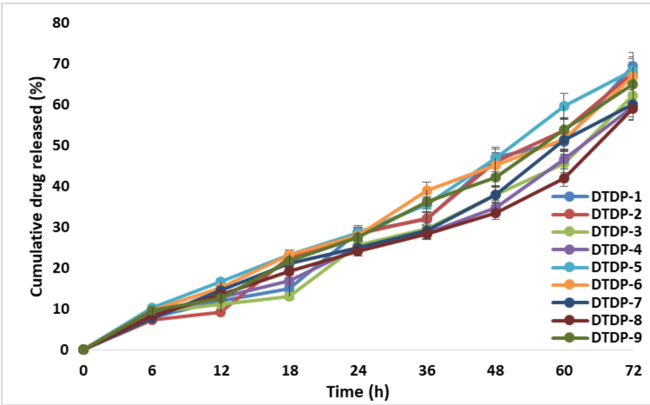

Figure 3: In-vitro DPZ permeation from the patch

Table 2: Fit Summary of the responses

Source	*Sequential p-value*	*Adjusted R^2*	*Predicted R^2*
Response 1: Folding endurance			
Linear	< 0.0001	0.9908	0.9832
2FI	0.7781	0.9891	0.9701
Quadratic	0.9634	0.9823	
Cubic	0.2858	0.9957	
Response 2: DP@24h			
Linear	0.0018	0.8381	0.7696
2FI	0.8896	0.8065	0.7294
Quadratic	0.0891	0.9357	
Cubic	0.4302	0.9643	

The *in-vitro* drug permeation studies exposed that the drug permeation was extended in a controlled manner for up to 72 hours. Among the formulations tested, DTDP-5 showed better permeation characteristics compared to others. This extended drug discharge profile suggests that DTDP-5 has the potential for sustained therapeutic efficacy, which could be beneficial for conditions requiring prolonged drug action, such as dysmenorrhea. These results highlight the effectiveness of the transdermal patch formulation in providing controlled and sustained drug delivery, offering advantages in terms of patient compliance and convenience. Further optimization of the formulation parameters could potentially enhance drug permeation and optimize therapeutic outcomes (Figure 3).

The responses, FE, and drying resistance at 24 hours (DR@24h), were analyzed using Design Expert software. The fit summary (Table 2) and ANOVA details (Table 3) were generated to assess the adequacy of the model and the significance of the factors influencing the responses.

The high F-value of 89.82 underscores the significance of the model, indicating that the results are unlikely to be due to random chance, with a mere 0.18% probability of such a large F-value occurring by noise alone. This strong statistical support advises that the model effectively captures the relationships between the variables. The significance of

Table 3: ANOVA for a Quadratic Model

Source	*Sum of Squares*	*df*	*Mean Square*	*F-value*	*p-value*	
Response 1: Folding Endurance						
Model	2062.44	5	412.49	89.82	0.0018	significant
A-HPMC K100	2060.72	1	2060.72	448.72	0.0002	
B-PVP K30	1.13	1	1.13	0.2450	0.6546	
AB	0.2500	1	0.2500	0.0544	0.8305	
A^2	0.2841	1	0.2841	0.0619	0.8196	
B^2	0.2841	1	0.2841	0.0619	0.8196	
Response 2: DP@24h						
Model	310.42	5	62.08	24.28	0.0124	significant
A-HPMC K100	278.62	1	278.62	108.95	0.0019	
B-PVP K30	0.8439	1	0.8439	0.3300	0.6059	
AB	0.1640	1	0.1640	0.0641	0.8164	
A^2	29.78	1	29.78	11.64	0.0421	
B^2	7.26	1	7.26	2.84	0.1907	

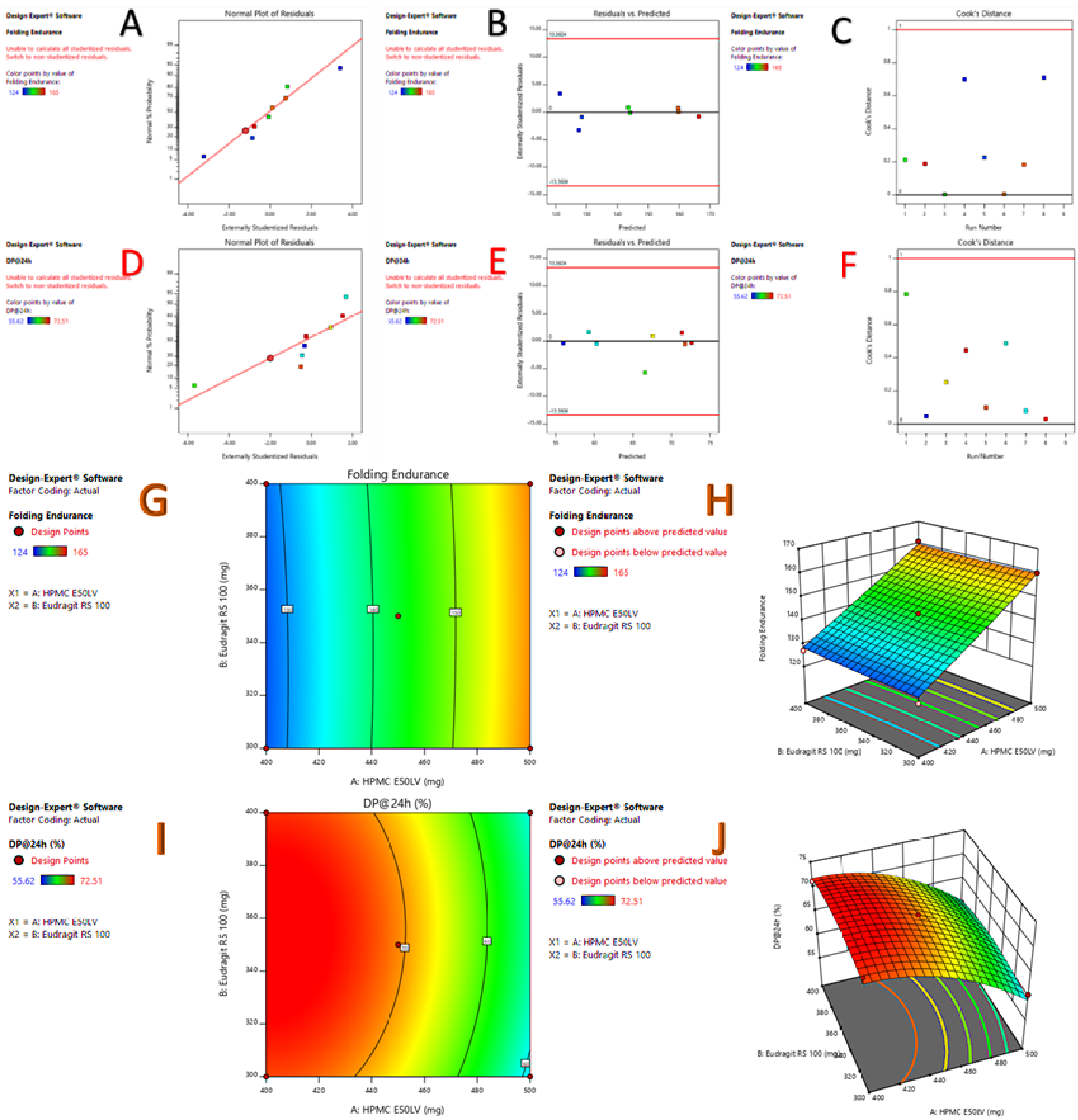

Figure 4: The impact of inputs on dependent variables: Normal (A&D), residual vs. predicted (B&E), Cooks distance (C&F) and Response surface plots (G, H, I&J)

model terms is further highlighted by their respective p-values, with those below 0.05 considered significant contributors to the model's predictive power. Notably, model term A emerges as significant, indicating its substantial impact on the response variables. Conversely, p-values exceeding 0.10 suggest insignificance, indicating that certain model terms do not significantly influence the outcomes. The second F-value of 24.28 similarly signifies the model's significance, with only a 1.24% chance of occurring by noise. This reinforces the reliability of the model in explaining the observed variation in the response variables. In practical terms, identifying and eliminating insignificant model terms while retaining essential ones to maintain hierarchy can enhance the model's efficiency and predictive accuracy. According to the final equation of FE, the factors are as follows:

$$FE=+143.00+16.05A+0.3750B-0.2500AB+0.3125A^2+0.3125B^2$$

By comparing the coefficients of the factors in the coded equation, one can assess their relative impact on the response variable. This facilitates a systematic evaluation of the influence of each factor and aids in identifying key determinants of the observed outcomes. The DP was judged as follows:

$$DP@24h=+70.32-5.87A+0.3523B+0.1475AB-3.01A^2-1.62B^2$$

The results of the FE and DR@24h responses corresponded closely with the graphical representations in Figures 4A and 4D. A strong correlation was observed between the residuals and the predicted values, as depicted in Figures 4B and 4E. Additionally, the cooking distances for FE and DR@24h were below the threshold indicated by the red line in Figures 4C and F, suggesting a good fit of the model. These figures provide 2D and 3D plots illustrating the response surfaces, which depict the relationship between the factors and the responses. Based on these results, it is evident that HPMC K100 and PVP K30 exert distinct effects on FE and DR@24h after 24 hours, highlighting their differential impact on the properties of the transdermal drug delivery patches.

CONCLUSION

In conclusion, the formulation of transdermal patches incorporating a blend of HPMC K100 and PVP K30, along with propylene glycol as a plasticizer, represents a promising approach for achieving controlled discharge of DPZ, through a comprehensive evaluation of the physical and chemical assets of the transdermal patches. It was observed that the developed patches exhibited satisfactory characteristics. Furthermore, *in-vitro* studies demonstrated prolonged drug permeation for up to 72 hours, with DTDP-5 showing superior permeation among the formulations tested. The statistical analysis using Design Expert software exposed significant model terms, emphasizing the importance of HPMC K100 and PVP K30 in influencing folding endurance and drying resistance after 24 hours. The close correlation between experimental results and predicted values, as evidenced by residual analysis, further validates the effectiveness of the formulated transdermal patches. Overall, these findings highlight the potential of the developed transdermal drug delivery system as a viable option for achieving controlled discharge of DPZ, offering opportunities for improved therapeutic outcomes in the management of conditions such as Alzheimer's disease.

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