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Original Article

Design Expert Optimization of Transdermal Patches for Effective Prolonged Release of Alzheimer's Medications

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ABSTRACT

Objectives: This study aimed to develop and characterize transdermal patches for Donepezil (DPZ) and Memantine (MMT) using a Box-Behnken Design (BBD), evaluating drug permeation at 8 hr, 16 hr, and 24 hr, with optimization through Design Expert software. **Materials and Methods:** The patches were formulated with HPMC K15, modified chitosan, and PVP K30. The physicochemical properties and drug infusion were tested and characterized. **Results:** The transdermal patches developed in this study were found to be soft and flexible, indicating good handling properties and potential for comfortable application. The patches demonstrated sustained drug release, extending beyond 24 hr, which is crucial for preserving consistent beneficial levels of DPZ and MMT in the systemic circulation. The optimal formulation, as identified through the BBD using Design Expert software, included HPMC K15 (125 mg), modified chitosan (65.91 mg), and PVP K30 (40 mg). This combination effectively facilitated prolonged drug penetration while keeping the flexibility and integrity of the patches. **Conclusion:** The study concludes that the formulated transdermal patches using HPMC K15, modified chitosan, and PVP K30 offer an effective means for prolonged delivery of DPZ and MMZ. The optimized patches support sustained discharge for a prolonged time, which can improve patient compliance and therapeutic outcomes in treating conditions like Alzheimer's disease. The use of a systematic design approach, such as the BBD, proved beneficial in optimizing the formulation parameters, ensuring the development of high-quality transdermal patches with desirable properties for clinical application.

Keywords: Box Behnken Design, Drug permeation, Extended release, Flexibility.

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INTRODUCTION

Alzheimer's Disease (AD) is a broadminded nervous complaint chiefly upsetting the elderly, leading to behavioral abnormalities, memory loss, and reasoning deterioration.[1] This leads to the formation of plaques, which obstruct neuronal communication and cause cell death.[2] Early symptoms include disorientation and difficulty recalling recent events. As the disease progresses, these symptoms worsen, significantly impacting daily activities and quality of life. Advanced stages of AD involve severe memory loss, language difficulties, disorientation, and notable behavioral and personality changes. While there is no cure for AD, various therapies can help manage symptoms and improve the quality of life for patients.[3] Research continues to focus on empathetic the fundamental mechanisms of the disease and developing more effective therapeutic strategies.

Transdermal drug delivery is a process that administers medication through the skin. This method utilizes transdermal patches that adhere to the skin, allowing medication to be delivered directly into the bloodstream with a controlled and continuous release.[4] By bypassing the gastrointestinal tract and hepatic first-pass metabolism, transdermal administration can reduce potential side effects and enhance drug absorption. This technique is particularly advantageous for medications that require constant plasma levels, as it enables steady and prolonged drug release.[5] Various polymers and enhancers are employed in the design of transdermal systems to optimize drug permeability and ensure skin compatibility. Applications of transdermal drug delivery include pain management, hormone replacement therapy, and the treatment of neurological disorders, providing a promising solution for improving patient compliance and therapeutic outcomes.[6]

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The cholinesterase inhibitor Donepezil (DPZ) functions by increasing the brain's concentration of acetylcholine. DPZ decreases the collapse of acetylcholine, thus elevating cholinergic transmission and supporting cognitive functions.[7] It is typically recommended for the mild to moderate stages of AD and has been revealed to improve behavior, daily activities, and cognitive abilities.[8]

Conversely, Memantine (MMZ) functions as an antagonist of the NMDA (N-methyl-D-aspartate) receptor. It works by modulating the activity of glutamate, a neurotransmitter essential for memory and learning.[9] In AD, extreme glutamate activity can lead to excitotoxicity, which injures neurons. By stabilizing glutamate activity, MMZ helps protect neurons from over-activation and may slow the progression of symptoms. It is often used in modest to austere stages of AD, either alone or in combination with cholinesterase inhibitors like DPZ.[10]

When combined, DPZ and MMZ provide a comprehensive strategy for addressing the neurochemical imbalances that contribute to AD. DPZ enhances cholinergic transmission by increasing acetylcholine levels, while MMZ protects neurons by stabilizing glutamate activity.[11] Together, they offer a more holistic approach to treatment, aiming to improve patients' functional abilities and quality of life.[12]

Modern optimization strategies such as factorial design and Quality by Design (QbD) provide significant advantages over conventional methods in various domains, including pharmaceutical research.[13] QbD emphasizes a methodical and proactive approach, focusing on understanding processes, identifying crucial quality traits, and minimizing risks to achieve greater quality and efficiency.[14] It promotes continual improvement, streamlines approval processes, and aligns with regulatory standards. The factorial design allows the simultaneous investigation of multiple components and their interactions, offering comprehensive insights and data-driven decisions that enhance process optimization.[15] By considering numerous factors and their interactions, factorial design and QbD are more effective, economical, and capable of producing reliable, high-quality results compared to the conventional one-factor-at-a-time method.[16]

The objective was to develop sustained-release patches that could effectively deliver DPZ and MMT using HPMC K15, modified chitosan, and PVP K30, and to evaluate drug permeation at 8 hr, 16 hr, and 24 hr, with the design optimized using Design Expert software.

MATERIALS AND METHODS

Materials

DPZ and MMZ were provided by Cipla Pharmaceuticals, Bangalore. Fischer Scientific supplied HPMC K15, modified chitosan, PVP K30, dichloromethane, and propylene glycol. The cellulose acetate membrane necessary for the patches was sourced from Chemtech India. All other chemicals and materials used were of AR grade.

Making of the patch

DPZ and MMZ patches were prepared using the solvent casting method with HPMC K15, modified chitosan, and PVP K30 dissolved in dichloromethane (25 mL). The mixture was enthused for 30 min with a magnetic stirrer, and then propylene glycol (1 mL) was added. DPZ/MMZ was then combined into the solution under incessant stirring. The resulting polymeric solution with DPZ (20 mg)/MMZ (20 mg) was poured into a petri dish and allowed to dry at room temperature for 6 hr. After drying, the patches were cut into 1x1 cm squares, wrapped in aluminum foil, and stored in desiccators until further use. A Box-Behnken design was employed to evaluate 15 different blends, using Design Expert Software (Version 13) to analyze DPZ/MMZ permeation at various intervals (DP@8 hr, DP@16 hr, and DP@24 hr)[17] (Table 1 and Figure 1).

Compatibility observations

Samples were blended with KBr to form pellets, which were subsequently scanned using an FTIR spectrophotometer across the range of 4000-400 cm^{-1}. Spectra were obtained and analyzed for significant shifts, peak disappearances, or the emergence of new peaks in comparison to the spectra of the pure drugs.

Appeal

The evaluation of all Transdermal Patches (TDP) included a detailed assessment of their color, clarity, flexibility, and smoothness, which was meticulously conducted using a magnifying lens to ensure thorough inspection. Additionally, the thickness of each patch was precisely measured using a screw gauge, ensuring accurate and consistent data collection across the samples. These evaluations are crucial in determining the physical attributes and quality parameters of the TDP, providing essential information for their further characterization and potential application in drug delivery systems.[18]

Weight variation

Each patch was separately weighed, and the mean weight of five patches was assessed by summing the weights of the individual samples and dividing by five. Uniformity in weight indicates consistent composition of the patches, which ensures there are no issues during packaging. This quality control measure helps to maintain the reliability and consistency of the transdermal patches, ensuring that each unit delivers the intended dosage effectively.[19]

Flexibility of the patches

The flexibility of each patch was assessed by folding them along the same plane until they cracked. This method provided a tangible measure of how well the patches could withstand bending without breaking, reflecting their ability to endure handling and application without compromising their structural integrity. Patches that exhibited greater resistance to cracking indicated higher flexibility, which is essential for ensuring they can conform to the contours of the skin during application while remaining intact. This evaluation is crucial in determining the overall quality and usability of the patches, ensuring patient comfort.[20]

Mechanical strength

To ensure the TDPs were securely supported within the patch holder, adhesive tape was affixed to one end, while a small pin inserted into the tape at the opposite end maintained its straight alignment and prevented deformation during expansion. To measure the TDP's tensile strength, a pulley system was employed: one end of a thread was fixed to a small pin on the patch, passed over a pulley, and weights were gradually added to the other end. As weights increased, a pointer traced the thread's movement on graph paper, with the breaking force of the patch determined by the weight at which it ruptured under tension. This method provided a precise assessment of the patch's mechanical resilience, ensuring it could withstand typical forces encountered during handling and application, thereby validating its durability for practical use.[21]

Assessing the moisture in the patches

The patches were placed in desiccators containing $CaCl_2$ to maintain a low-humidity environment, facilitating moisture absorption from the surroundings and establishing a dry atmosphere around the samples. This procedure involved periodically weighing the patches at predetermined intervals. Initially, the patches were weighed while wet, including any moisture content present. Subsequently, the patches underwent drying to eliminate moisture. Once consecutive weighing showed no further weight loss, indicating stabilization, the patches were considered dry. The variance between the first wet weight and the stabilized dry weight of the patches represented the amount of moisture initially present. This meticulous drying process ensured accurate determination of the patches' moisture content, crucial for preserving their stability and quality during storage and use (E.q.1).[22]

$$\text{Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} X100 \text{---} (1)$$

Drug content

The TDPs were cut (1x1 cm^2) and placed in 100 mL of phosphate buffer in a beaker, where they were agitated to facilitate drug release into the solution. The resulting solution was then filtered (Whatman filter paper) to remove any particulate matter, and the absorbance of the filtrate was checked at 271 nm for DPZ and 354 nm for MMZ using a UV spectrophotometer. These absorbance measurements allowed for quantification of the released DPZ and MMZ from the patches, providing essential data on drug release kinetics and efficiency.[23,24]

Drug Diffusion Study

A Franz diffusion cell system was utilized to assess the permeation of drugs through a cellophane membrane. Phosphate buffer solution with a pH of 7.4 served as the medium, simulating physiological conditions. The diffusion of the drug through the membrane was evaluated spectrophotometrically. The system was maintained at a constant temperature of 32°C using a water bath. Sampling from the diffusion cell was conducted at regular intervals: at 8 hr, 16 hr, and 24 hr, ensuring consistent conditions throughout the experiment. These sampling points allowed

Table 1: Different independent variables and the dependent variables used in the investigation.

Independent variables	Levels		
	Low	Medium	High
X_1=HPMC K15 (mg)	100	125	150
X_2=Modified chitosan 80 (mg)	100	150	200
X_3=PVP K30 (mg)	30	40	50
Distorted values	-1	0	+1
Responses observed	Conditions		
Y_1=DDP@8 hr (Donepezil drug permeation at 8 hr).	Maximize		
Y_2=DDP@16 hr (Donepezil drug permeation at 16 hr).	Maximize		
Y_3=DDP@24 hr (Donepezil drug permeation at 24 hr).	Maximize		
Y_4=MDP@8 hr (Memantine drug permeation at 8 hr).	Maximize		
Y_5=MDP@16 hr (Memantine drug permeation at 16 hr).	Maximize		
Y_6=MDP@24 hr (Memantine drug permeation at 24 hr).	Maximize		

for the measurement of drug permeation kinetics over time, providing crucial data on the release profile and efficiency of the transdermal patches.[25]

RESULTS

The distinguishing peaks of DPZ and MMZ endured unchanged when united with various excipients, indicating no significant interactions or chemical reactions. This preservation of the structural integrity of DPZ and MMZ confirms their compatibility with the selected excipients, ensuring the maintenance of their efficacy and stability (Figures 2 and 3).

The prepared transdermal patches were observed to be thin, translucent, and free from air bubbles and gaps, indicating high-quality fabrication. The thickness of the patches was uniform, ranging from 39.36±0.87 mM to 42.85±0.64 mM, with TDP-8 being the thinnest among the formulations. Weight uniformity was also consistent across all patches, ranging from 707.74±1.25 mg (TDP-6) to 723.53±5.62 mg (TDP-8). Minor variations in weight were attributed to the different proportions of ingredients used in each formulation. Flexibility tests showed that all patches exhibited excellent flexibility, with folding endurance exceeding 160 in all formulations. Notably, TDP-12 demonstrated the highest folding endurance, breaking at 188±2 folds, likely due to its higher modified chitosan content. Moisture content in the patches was minimal, not exceeding 3.35% in any formulation. The tensile strength of the patches was also commendable, with TDP-10 exhibiting the highest tensile strength at 0.588±0.01 mg/cm²/h, which could be attributed to its higher HPMC K15 content. Additionally, all patches demonstrated good drug retention, holding more than 90% of the DPZ and MMZ content (Table 2).

In vitro DPZ/MMZ permeation

In vitro DPZ/MMZ permeation observations were made to judge the sustained release properties of the various patches. The results revealed consistent DPZ/MMZ permeation across all patches, confirming their ability to maintain a steady discharge of the drugs. Notably, formulation TDP-11, which included HPMC (125 mg), PVP K30 (40 mg), and modified chitosan (65.91 mg), exhibited superior DPZ/MMZ permeation compared to the other formulations. This enhanced permeation suggests that the specific combination of ingredients in TDP-11 contributed to its improved performance in facilitating the sustained release of DPZ and MMZ (Figure 4).

Model Fit summary

The analysis of the responses (DPZ permeation at 8 hr, 16 hr, and 24 hr, and MMZ permeation at 8 hr, 16 hr, and 24 hr) using Design Expert software yielded the fit summary (Table 3). The software's analysis helps to refine the model by reducing the number of insignificant terms while maintaining the hierarchy of the model. This approach ensures the final model is both parsimonious and effective in describing the data. The final equation for the responses is as follows:

$$DDP@8\ hr = +26.49 - 0.36A - 1.74B - 0.182C - 0.034AB - 0.04AC - 0.07BC + 0.168A^2 - 0.12B^2 + 0.12C^2$$

$$DDP@16\ hr = +40.01 - 1.17A - 5.18B - 0.294C - 0.61AB - 0.22AC + 0.01BC + 0.213A^2 + 0.39B^2 + 0.57C^2$$

$$DDP@24\ hr = +63.8 - 0.72A - 4.15B - 0.4036C + 0.04AB + 0.11AC + 0.07BC - 0.05A^2 + 0.07B^2 + 0.18C^2$$

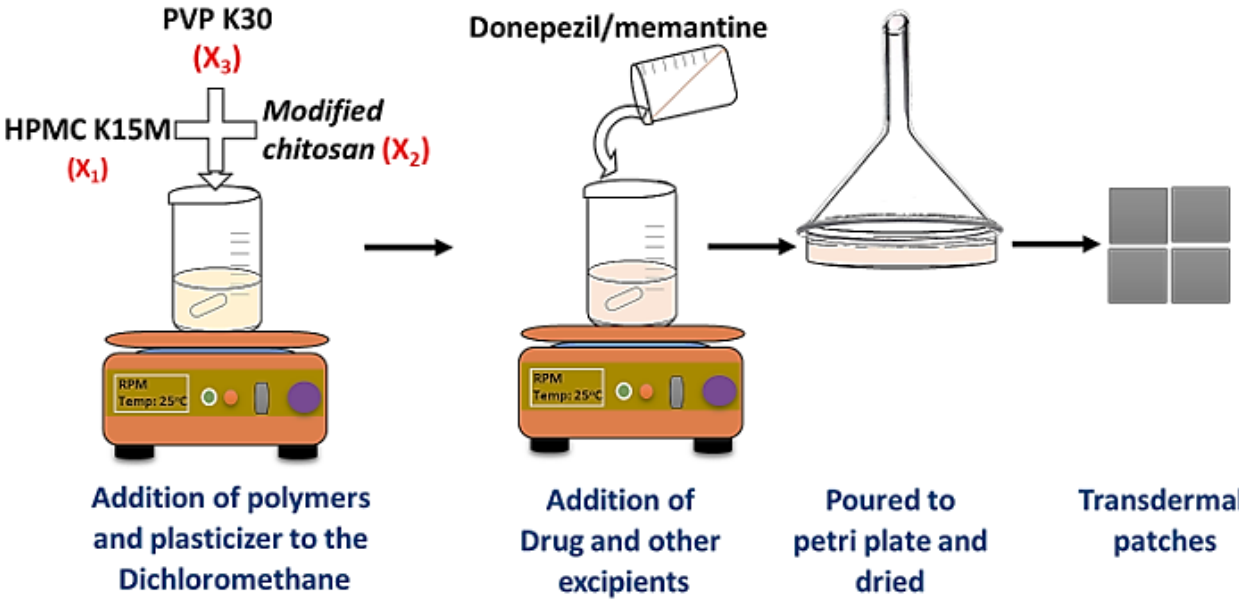

Figure 1: Flow diagram of TDPs preparation.

Table 2: Physicochemical of TDPs.

Trial	Appeal	Thickness (mM)	UW (mg)	FE	MC (%)	TS (mg/cm²/h)	DPZ content (%)	MMZ content (%)
TDP-1	Very good	42.85±0.64	709.80±1.35	166±5	3.13±0.03	0.544±0.02	92.39±2.36	90.39±2.36
TDP-2	Very good	41.02±0.81	711.51±2.05	181±2	3.27±0.06	0.576±0.02	93.53±5.67	92.53±5.67
TDP-3	Very good	42.21±1.03	723.04±3.98	185±6	3.35±0.04	0.537±0.01	93.32±2.52	93.32±4.81
TDP-4	Very good	41.11±0.65	716.74±1.75	182±4	3.25±0.02	0.579±0.01	94.62±3.48	94.62±3.16
TDP-5	Very good	42.12±2.36	714.28±0.64	165±8	3.26±0.02	0.541±0.01	96.51±2.58	95.51±2.14
TDP-6	Very good	39.63±0.81	707.74±1.25	176±6	3.24±0.05	0.579±0.03	96.84±2.08	94.84±3.68
TDP-7	Very good	40.27±0.82	707.84±2.61	183±3	3.31±0.02	0.529±0.04	97.62±3.59	96.62±2.67
TDP-8	Very good	39.36±0.87	723.53±5.62	185±4	3.28±0.03	0.575±0.02	93.58±2.27	95.58±2.95
TDP-9	Very good	42.51±0.94	714.03±6.62	174±2	3.31±0.02	0.569±0.02	96.21±2.94	96.65±1.14
TDP-10	Very good	40.78±0.11	715.98±8.34	173±3	3.23±0.03	0.588±0.01	94.85±1.95	97.15±2.67
TDP-11	Very good	41.64±0.74	711.68±5.25	177±2	3.28±0.02	0.564±0.02	99.23±0.12	98.07±5.02
TDP-12	Very good	40.69±0.05	709.07±4.40	188±2	3.19±0.02	0.567±0.01	98.29±5.16	94.54±4.67
TDP-13	Very good	39.44±0.41	708.97±7.75	179±1	3.27±0.03	0.571±0.02	97.33±3.84	93.62±2.95
TDP-14	Very good	41.30±0.95	709.65±9.62	175±3	3.17±0.02	0.535±0.03	93.52±3.65	91.52±2.85
TDP-15	Very good	41.24±0.10	710.51±2.01	173±4	3.23±0.04	0.536±0.01	98.81±1.25	96.02±1.28

UW: Uniformity of weight; FE: Folding endurance; MC: Moisture content; TS: Tensile strength; DPZ: Donepezil; MMZ: Memantine; values in Mean±SD; trials (*n*)=3.

$$MDP@8\ hr=+29.01-0.36A-1.43B-0.12C-0.013AB-0.11AC+0.01BC+0.326A^2+0.48B^2+0.31C^2$$

$$MDP@16\ hr=+35.0-0.74A-3.59B-0.582C+0.14AB+0.112AC-0.03BC+2.71A^2+2.62B^2+2.98C^2$$

$$MDP@24\ hr=+63.99-0.58A-2.82B-0.516C+0.10AB+0.02AC+0.10BC+1.58A^2+1.9B^2+1.96C^2$$

The responses (DDP@8 hr, DDP@16 hr, DDP@24 hr, MDP@8 hr, MDP@16 hr, and MDP@24 hr) in points matched the graphs in Figures 3 and 4. There was a close correlation between the residuals and the predicted appraisals, indicating the accuracy and reliability of the model generated by Design Expert software. The residual and predicted values were in good agreement, demonstrating that the model could effectively capture the variability in the experimental data and predict the responses accurately.

The Model F-values of 140.46, 483.15, 1805.71, 93.05, 80.95, and 37.13 indicate highly significant models, with only a 0.01% provision that these values may be owing to noise. The associated *p*-values below 0.05 identify significant model terms, specifically: A, B, and C in the first model; A, B, C, AB, B^2, and C^2 in the second model; and A, B, C, A^2, B^2, and C^2 in the third model. Conversely, terms with *p*-values above 0.1 are considered non-significant; suggesting that model reduction could be beneficial if many such terms are present.

Residuals versus predicted values for the responses were shown in Figure 5 (A, C, E, G, I and K), illustrating the accuracy of the model predictions. Cook's distance, depicted in Figure 4 (B, D, F, H, J and L), represents the influence of individual data points

on the model, highlighting the impact of input factors on the response.

Contour plots for the outputs are shown in Figure 4, illustrating the permeation of DPZ and MMZ at various time points: Figure 6 A) DDP@8 hr, B) DDP@16 hr, C) DDP@24 hr, D) MDP@8 hr, E) MDP@16 hr, and F) MDP@24 hr. Additionally, the 3D response surface plots for these outputs were displayed in Figure 7, providing a more comprehensive visualization of the drug permeation dynamics: A) DDP@8 hr, B) DDP@16 hr, C) DDP@24 hr, D) MDP@8 hr, E) MDP@16 hr, and F) MDP@24 hr.

DISCUSSION

The FTIR spectra provided clear evidence of this compatibility, which is essential for developing a stable and effective pharmaceutical formulation. Specifically, the IR spectra showed no changes in peaks and stretches when DPZ and MMZ were mixed with HPMC K15, modified chitosan, and PVP K30, indicating no physical interaction between the drugs and these polymers. According to Madan (2015), FTIR spectral studies demonstrated that DPZ is compatible with HPMC.[26]

The results indicate that the transdermal patches were successfully fabricated with desirable physical characteristics such as thinness,

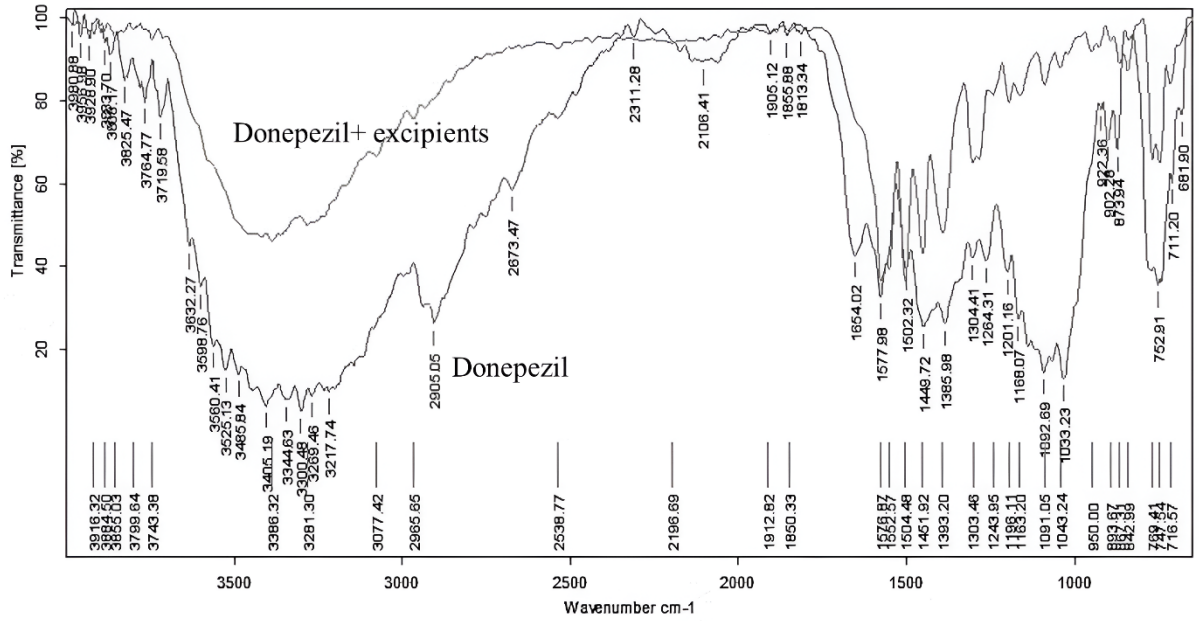

Figure 2: FTIR spectra of DPZ and its excipients.

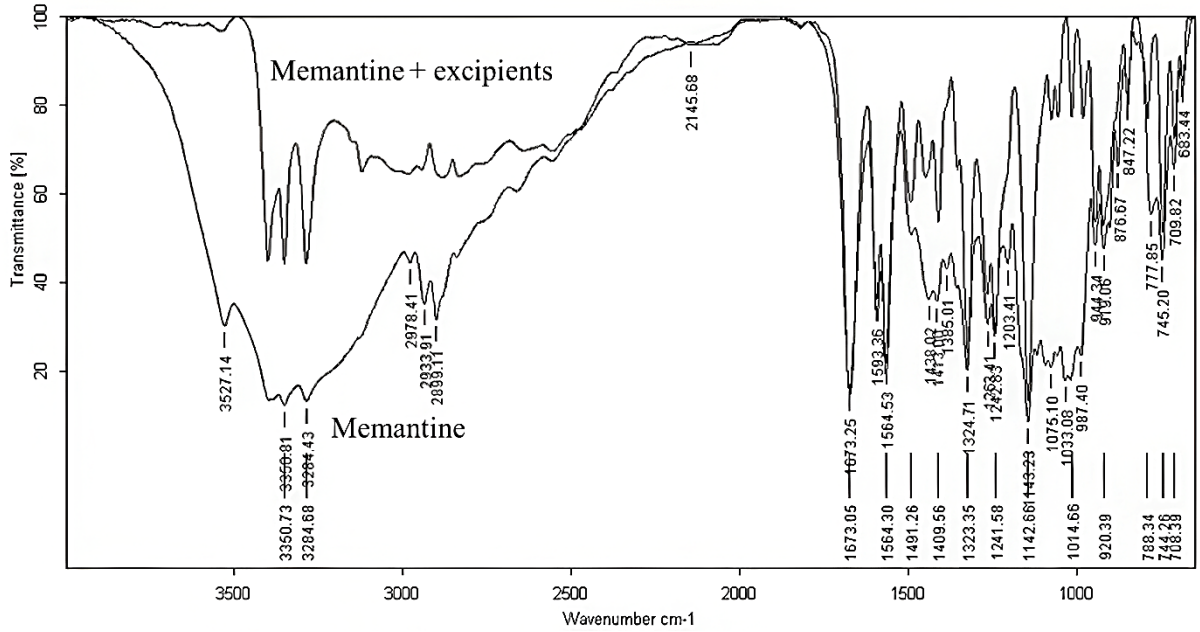

Figure 3: FTIR spectra of MMZ and its excipients.

Table 3: Fit Summary of the dependent variables.

Source	Sequential *p*-value	Adjusted R^2	Predicted R^2
Response 1: DDP@8 hr			
Linear	<0.0001	0.9716	0.9578
2FI	0.9084	0.9633	0.9474
Quadratic	0.0291	0.9890	0.9633
Cubic	0.2000	0.9990	0.9781
Response 2: DDP@16 hr			
Linear	<0.0001	0.9802	0.9721
2FI	0.0771	0.9879	0.9840
Quadratic	0.0215	0.9968	0.9896
Cubic	0.1754	0.9998	0.9951
Response 3: DDP@24 hr			
Linear	<0.0001	0.9965	0.9948
2FI	0.5071	0.9963	0.9945
Quadratic	0.0156	0.9991	0.9973
Cubic	0.1094	1.0000	0.9995
Response 1: MDP@8 hr			
Linear	<0.0001	0.9304	0.9209
2FI	0.9130	0.9101	0.8983
Quadratic	0.0089	0.9834	0.9432
Cubic	0.2238	0.9981	0.9586
Response 2: MDP@16 hr			
Linear	0.0014	0.6719	0.6802
2FI	0.9983	0.5507	0.5586
Quadratic	0.0002	0.9809	0.9352
Cubic	0.2207	0.9979	0.9538
Response 3: MDP@24 hr			
Linear	0.0005	0.7320	0.7257
2FI	0.9975	0.6335	0.5865
Quadratic	0.0026	0.9587	0.8778
Cubic	0.1286	0.9985	0.9664

translucency, and absence of air bubbles and gaps. The uniformity in thickness and weight suggests consistent quality and reproducibility in the patch preparation process, despite minor variations due to differing ingredient proportions. The high folding endurance across all formulations highlights the excellent flexibility of the patches, essential for practical application and durability during use. The outstanding performance of TDP-12 in folding endurance can be attributed to its higher modified chitosan content, which enhances flexibility. Minimal moisture content in the patches is beneficial as it lessens the risk of microbial growth and ensures a longer shelf life. The superior tensile strength observed in TDP-10 underscores the reinforcing effect of higher HPMC K15 content, which contributes to the mechanical strength of the patches. The high retention of DPZ and MMZ content in all patches confirms the efficiency of the formulation in maintaining drug stability and potency, ensuring effective transdermal delivery. Overall, these findings demonstrate the fruitful enlargement of robust and effective TDP suitable for sustained drug delivery. In 2022, Nunes *et al*., conducted a study in which DPZ patches were formulated using a combination of biocompatible polymers, including chitosan, gelatin, collagen, and HPMC. This combination was aimed at improving the drug's delivery and efficacy.[27]

The consistent permeation of DPZ and MMZ across all patches indicates that the formulations were successful in achieving sustained drug release, which is critical for preserving the beneficial planes of the drugs over an extended period. The

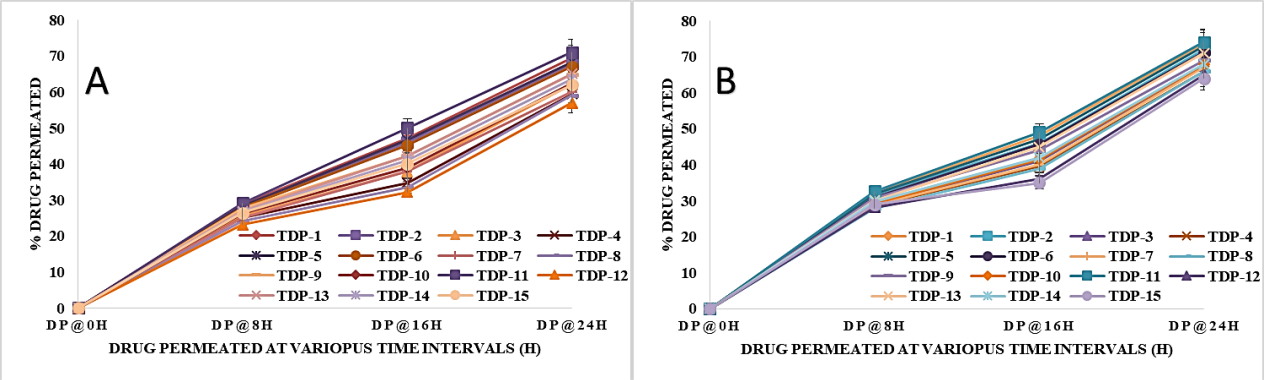

Figure 4: *In vitro* drug permeation from the patches A) for DPZ and B) for MMZ.

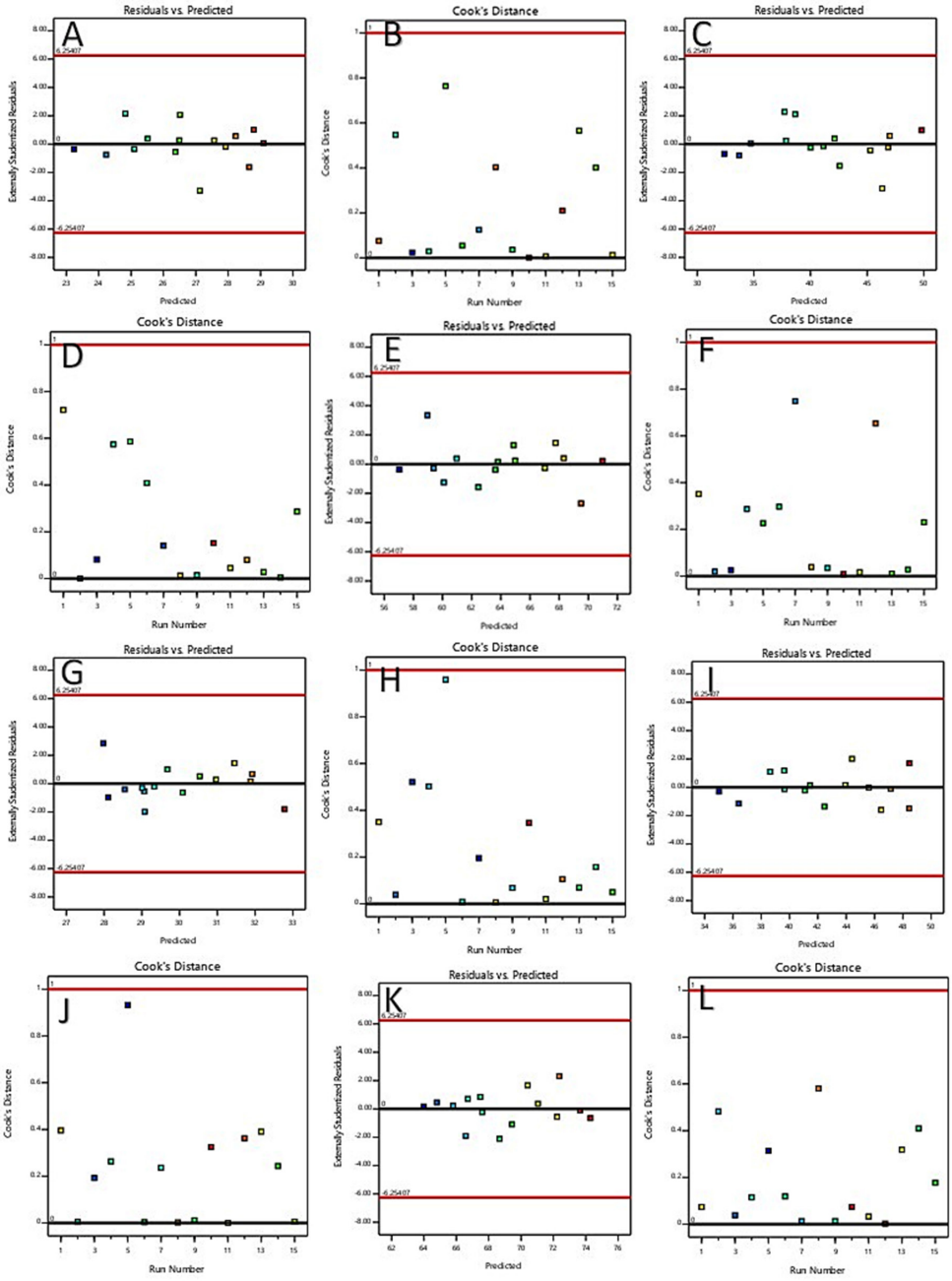

Figure 5: Residual vs. predicted (A, C, E, G, I and K), Cooks distance (B, D, F, H, J, and L) representing the impact of input factors on the response.

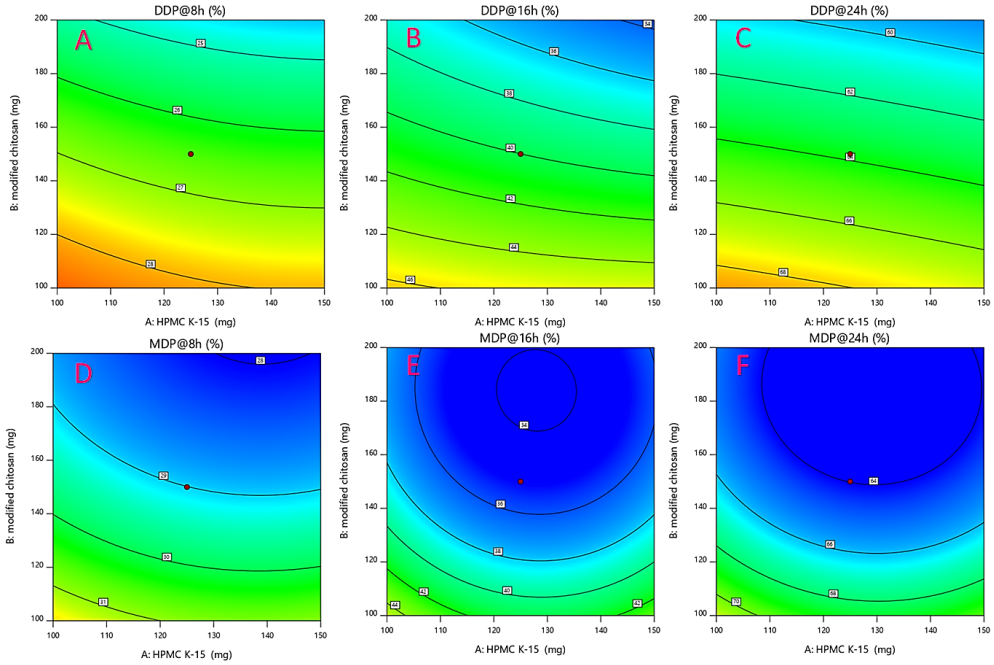

Figure 6: Contour plots for the outputs for A) DDP@8 hr; B) DDP@16 hr; C) DDP@24 hr; D) MDP@8 hr; E) MDP@16 hr; F) MDP@24 hr.

superior performance of TDP-11 in particular highlights the effectiveness of the specific combination of HPMC, PVP K30, and modified chitosan in enhancing drug permeation. HPMC is known for its film-forming properties and ability to control drug release, while PVP K30 can enhance the solubility and bioavailability of drugs. Modified chitosan contributes to improved permeability, which likely synergized with the other components to boost DPZ and MMZ permeation in TDP-11. These findings underscore the importance of optimizing the composition of transdermal patches to achieve the desired drug release profile, ensuring both efficacy and patient compliance in drug delivery systems.

The near association among the residuals and the predicted values underscores the robustness and precision of the model in predicting the drug permeation profiles. Residual analysis is a crucial step in model validation, as it helps to identify any discrepancies between observed and predicted values. The minimal differences between the residuals and predicted appraisals suggest that the model's assumptions were met and that it can reliably simulate the actual experimental outcomes. This high level of agreement not only validates the model but also enhances confidence in its use for optimizing the formulation parameters. By accurately predicting drug permeation, the model provides a valuable tool for further refinement and development of effective transdermal patches, ensuring consistent drug delivery and therapeutic efficacy.

The substantial Model F-values confirm the statistical significance and robustness of the developed models, demonstrating that the observed variations in drug permeation responses are well-explained by the models rather than random noise. The *p*-values below 0.05 indicate that the factors A, B, and C, as well as interaction and quadratic terms in certain models, significantly influence the drug permeation outcomes. This insight is critical for understanding which formulation variables most impact drug release profiles and should be prioritized in further optimization efforts.

The presence of non-significant terms, denoted by *p*-values above 0.1, suggests potential for model simplification. Reducing these terms can streamline the model, making it more parsimonious without sacrificing predictive accuracy. This approach helps in focusing on the most influential factors, thereby improving the efficiency of the optimization process. The refined models, with only significant terms retained, provide a clearer understanding of the key drivers of drug permeation and enhance the reliability of the predictive equations. These findings guide the formulation of transdermal patches with optimized drug release characteristics, ensuring effective and sustained delivery of DPZ and MMZ. MK Chauhan and PK Sharma employed Box-Behnken Design (BBD) for rivastigmine patches.[28]

The residuals versus predicted plots in Figure 4 (A, C, E, G, I and K) provide a clear visual representation of the model's predictive accuracy. These plots help identify any systematic deviations or patterns, ensuring that the residuals are randomly distributed around zero, which indicates a good fit for the model. A close clustering of residuals around the zero line proposes that the model forecasts are precise and that there are no major discrepancies between the observed and predicted values.

Cook's distance plots, shown in Figure 4 (B, D, F, H, J and L), offer insight into the influence of individual data points on the overall

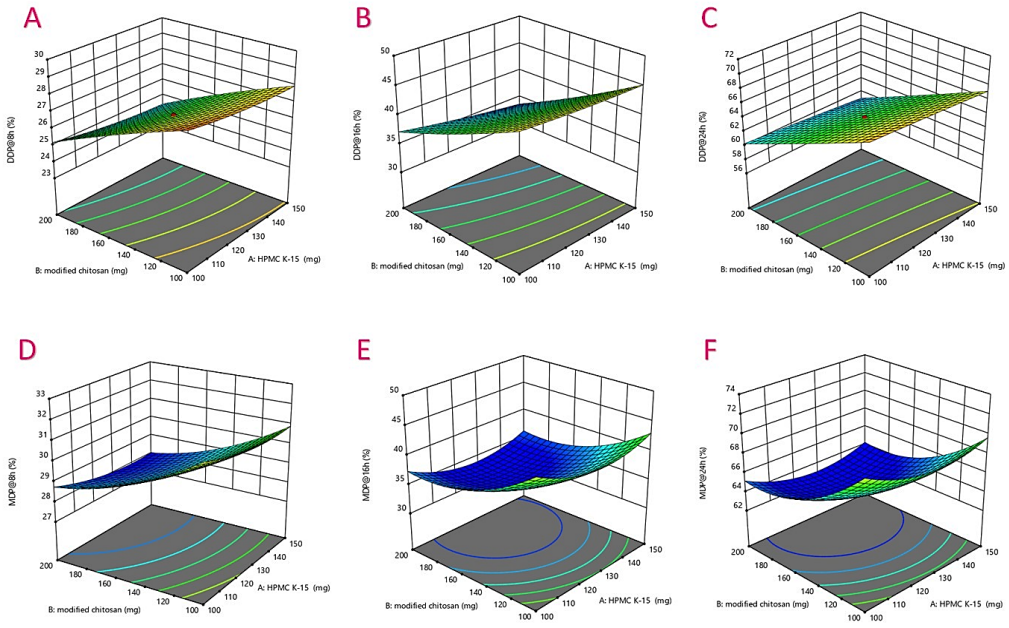

Figure 7: 3D response surface plots for the outputs for A) DDP@8 hr; B) DDP@16 hr; C) DDP@24 hr; D) MDP@8 hr; E) MDP@16 hr; F) MDP@24 hr.

model. Points with high Cook's distance values designate possible outliers or powerful comments that excessively disturb the model's parameters. By identifying these points, researchers can assess whether any specific input factors have an undue impact on the response and consider whether they need to be addressed or excluded from the model. Together, these diagnostic plots validate the robustness of the model and its ability to accurately predict drug permeation responses. They also highlight the critical input factors that significantly influence the responses, guiding further refinement of the formulation. By ensuring that the residuals are well-distributed and that no single data point unduly influences the model, researchers can confidently rely on the model for optimizing transdermal patch formulations for sustained and effective delivery of DPZ and MMZ.

The contour plots in Figure 4 and the 3D response surface plots in Figure 5 offer valuable insights into the drug permeation behavior of the transdermal patches over time. These visualizations highlight the influence of formulation variables on the permeation rates of DPZ and MMZ at different intervals, helping to identify optimal conditions for sustained drug release. The contour plots provide a two-dimensional representation of the relationship between two independent variables and their combined effect on drug permeation at specific time points. These plots help to quickly identify regions of maximum and minimum response, facilitating the understanding of how variations in the formulation components affect drug release. Valeveti and Pashikanti (2023) designed, developed, and evaluated transdermal patches containing MMZ using the BBD. They highlighted the significance of the polymer system on the performance of the drug in a transdermal patch, aiming to create a safe and effective delivery system for DPZ.[29]

The 3D response surface plots, on the other hand, offer a three-dimensional perspective, allowing for a more detailed exploration of the interactions between multiple variables and their collective impact on drug permeation. These plots help visualize the response surface curvature and identify the optimal combination of variables that maximize drug permeation at each time point.

Together, the contour and 3D response surface plots validate the significance of the identified model terms and provide a clear depiction of the formulation landscape, guiding the optimization process. By leveraging these visual tools, researchers can fine-tune the formulation parameters to achieve desired drug release profiles, ensuring effective and sustained delivery of DPZ and MMZ through the transdermal patches.

CONCLUSION

The transdermal delivery system for Donepezil (DPZ) and Memantine (MMZ) utilizes a combination of HPMC K15, modified chitosan, and PVP K30, demonstrating the potential for sustained release of these drugs from matrix-type transdermal patches. HPMC K15, a cellulose derivative, acts as a matrix former and helps control the discharge rates of DPZ and MMZ. PVP K30 and modified chitosan enhance the solubility and bioavailability of DPZ and MMZ. This combination aims to achieve controlled discharge through the skin, ensuring extended release over a desired period. Matrix-type transdermal patches release DPZ and MMZ from a polymer matrix directly in contact with the skin,

offering a promising solution for maintaining consistent drug levels and improving therapeutic outcomes.

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ABBREVIATIONS

AD: Alzheimer's disease; **NMDA:** N-methyl-D-aspartate; **DPZ:** Donepezil; **MMZ:** Memantine; **HPMC:** Hydroxypropyl methylcellulose; **PVP:** Polyvinylpyrrolidone; **QbD:** Quality by Design; **DP:** Donepezil drug permeation; **MM:** Memantine drug permeation; **TDP:** Transdermal patches; **FTIR:** Fourier-transform infrared spectroscopy; **TDP:** Transdermal Patch; **$CaCl_2$:** Calcium chloride; **AR grade:** Analytical reagent grade; **DPZ/MMZ:** Donepezil/Memantine; **UV:** Ultraviolet.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This study aimed to develop and characterize transdermal patches for Donepezil (DPZ) and Memantine (MMT) using a Box-Behnken design and optimization through Design Expert software. The patches were formulated with HPMC K15, modified chitosan, and PVP K30, and their physicochemical properties and drug permeation were tested and characterized. The results indicated that the developed transdermal patches were soft and flexible, suitable for comfortable application, and demonstrated sustained drug release extending beyond 24 hr. The optimal formulation, identified as HPMC K15 (125 mg), modified chitosan (65.91 mg), and PVP K30 (40 mg), effectively facilitated prolonged drug permeation while maintaining patch flexibility and integrity. The study concludes that these transdermal patches offer an effective means for the prolonged delivery of DPZ and MMT, potentially improving patient compliance and therapeutic outcomes for Alzheimer's disease. The systematic design approach, such as the Box-Behnken design, proved beneficial in optimizing formulation parameters, and ensuring the development of high-quality transdermal patches for clinical use.

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