Transdermal Patch Administration of Piroxicam Without Causing Gastric Irritation: A Factorial Design Approach

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Abstract

The information provided discusses the potential benefits of transdermal patches as an alternative route of drug administration to overcome the side effects associated with the oral administration of Piroxicam (PXM). Transdermal patches allow for efficient systemic delivery of drugs by bypassing hepatic first-pass metabolism and continuously releasing the drug into the bloodstream through intact skin. The study highlights the development of transdermal patches containing PXM using the solvent casting technique, utilizing film-forming polymers like Hydroxypropyl Methylcellulose (HPMC) E50LV and Eudragit RS 100, along with glycerin as a plasticizer. Drug-excipient interaction studies using Fourier Transform Infrared Spectroscopy (FTIR) are conducted to ensure the compatibility and stability of the drug and patch components. The aim of developing transdermal patches is to improve drug delivery, minimize side effects, and enhance the solubility and absorption of Piroxicam. By bypassing the gastrointestinal tract, transdermal patches potentially reduce gastrointestinal side effects and improve patient compliance. Various physical properties of the transdermal patches, such as appearance, weight difference, moisture content, tensile strength, and PXM content, are observed to be satisfactory. The study suggests that the combination of HPMC E50LV (400 mg) and Eudragit RS 100 (300 mg) with glycerin as a plasticizer can promote the release of PXM from the transdermal patches. Overall, the

development of transdermal patches offers a promising approach to improve drug delivery and minimizing side effects associated with oral administration of Piroxicam.

Keywords: Factorial design. Patch, Permeation, Polymer, Release,

Introduction

Transdermal drug delivery systems (TDDS) provide numerous advantages compared to conventional routes of administration. These include the avoidance of first-pass metabolism, improved patient comfort and convenience, sustained release of the drug, enhanced patient compliance, and reduced side effects(1). However, it is important to note that not all drugs are suitable for TDDS(2). The molecular properties and therapeutic requirements of the drug must be considered before deciding on the transdermal route. Factors such as drug solubility, molecular weight, and lipophilicity play a crucial role in determining the feasibility of TDDS(3). The formulation and design of TDDS require careful consideration to ensure optimal drug release, skin permeation, and stability(4, 5). Various techniques and technologies are employed to enhance drug permeation through the skin, such as the use of permeation enhancers, microneedles, and iontophoresis. Extensive research has been conducted on the transdermal route for the delivery of lipophilic drugs into the systemic circulation. Lipophilic drugs have a higher affinity for the lipid-rich stratum corneum layer of the skin, making them more amenable to transdermal delivery(6, 7). Overall, TDDS offers significant advantages in terms of improved patient compliance, reduced side effects, and sustained drug release. However, careful consideration of drug properties and formulation design is necessary to ensure the success of transdermal delivery.

Non-steroidal anti-inflammatory drugs (NSAIDs), including piroxicam (PXM), are commonly used to treat dysmenorrhea by reducing inflammation and relieving pain. However, oral administration of NSAIDs can cause gastric upset. Transdermal drug delivery systems (TDDS) offer a controlled and sustained release of medication over an extended period, ensuring continuous pain relief without the gastrointestinal side effects associated with oral intake(8).

By delivering the medication directly through the skin, TDDS provides improved patient comfort and convenience, eliminating the need for frequent dosing or swallowing pills. In the case of piroxicam, which is typically available in tablet form, the TDDS serves as an alternative route of administration for dysmenorrhea treatment, reducing side effects and improving patient compliance(9). The TDDS containing piroxicam were subjected to in vitro testing to evaluate their controlled release characteristics(10). Experimental studies have

shown that piroxicam is a promising candidate for controlled-release formulations, such as TDDS. Hydroxypropyl Methylcellulose (HPMC) E50LV and HPMC E50LV matrix polymers were utilized in the formulation to regulate the release of piroxicam from the patches. Overall, the TDDS of piroxicam provides a potential solution for controlled drug release, improving the efficacy and safety of dysmenorrhea treatment compared to the oral administration of NSAIDs. Further research and development in this area can contribute to enhancing patient outcomes and satisfaction(11, 12).

Traditional research methods often examine the impact of one variable at a time, primarily due to the ease of manipulation and analysis. However, studying individual factors in isolation can lead to false results because variables are often interdependent. To overcome this limitation, multivariate analysis combined with a design of experiments (DOE) is necessary. DOE allows researchers to systematically study the influence of multiple factors simultaneously, providing a more comprehensive understanding of their interactions and effects(13, 14).

DOE is widely used in product development to optimize product formulations, improve product quality, and identify the critical factors that affect product performance. It helps in identifying the optimal combination of ingredients or components and their levels to achieve desired product attributes(15). DOE is used to optimize manufacturing processes by identifying the key process parameters and their optimal settings. It helps in improving process efficiency, reducing variability, and minimizing defects or failures(10). DOE can be applied to various processes, such as chemical manufacturing, semiconductor fabrication, and food processing. DOE is employed to improve product or process quality by identifying and reducing sources of variation. It helps in determining the critical quality parameters and optimizing their levels to achieve desired quality targets(16). DOE can be used in quality control, Six Sigma projects, and continuous improvement initiatives. DOE is extensively used in scientific research to investigate the effects of multiple factors on a response variable. It allows researchers to systematically vary and control the factors of interest, ensuring efficient use of resources and providing reliable results. DOE is applied in fields like pharmaceutical research, agricultural studies, and environmental research. DOE can be used to assess and improve the reliability of products or systems(17, 18). It helps in identifying the critical factors that affect reliability and optimizing their settings to enhance product performance and durability. DOE techniques like accelerated life testing and reliability growth analysis are employed in this context. DOE can be applied in marketing and consumer research to understand consumer preferences and optimize marketing strategies(19). It helps in

identifying the factors that influence consumer behavior and determining the optimal levels of these factors to maximize consumer satisfaction and sales. DOE is used to optimize supply chain processes by identifying critical factors that impact supply chain performance, such as lead time, inventory levels, and transportation costs. It helps in determining the optimal configurations and settings of supply chain components to minimize costs and maximize efficiency(20, 21).

In the case of the study mentioned, the authors used Design Expert software (Version 11) to incorporate polymer concentration as a factor and assess the folding endurance and drug discharge at 24 hours (DR@24h) as responses(22). By using DOE, researchers can better capture the complex relationships between variables and obtain more accurate and reliable results. It allows for a more comprehensive evaluation of the impact of various factors on the desired outcomes, leading to a more informed decision-making process and enhanced understanding of the system under study(23).

2. Material and methods

2.1. Materials

Waksman Selman Pharmaceuticals, in Anantapur, donated piroxicam. Both HPMC E50LV and HPMC E50LV came from Mumbai's SD Fine Chem Ltd. We purchased a cellulose acetate membrane from Chemtech International in India. Other compounds were all of the analytical variety.

2.2. Methods

The solvent casting method was used to prepare transdermal drug delivery systems (TDDS) containing Piroxicam (PXM). HPMC E50LV and HPMC E50LV were dissolved in a solvent system of ethanol and DCM (2:1) in selected ratios. Glycerin was added to the solution and mixed for 30 minutes using a magnetic stirrer. PXM was then incorporated into the solution by continuous agitation(24, 25). The polymeric solutions containing PXM were cast in a petri dish and dried at room temperature for 6 hours(26, 27). The dried TDDS patches (PTDP) were cut into 1x1 cm2 squares and packed in aluminum foil for storage (Table 1, and Figure 1).

Table 1. Different formulae used in the study

Formulation	Piroxicam (mg)	HPMC E50LV (mg)	Eudragit RS 100 (mg)	Dichloromethane (ml)	Glycerin (ml)
PTDP-1	50	400	300	15	1.5
PTDP-2	50	500	300	15	1.5
PTDP-3	50	400	400	15	1.5
PTDP-4	50	500	400	15	1.5
PTDP-5	50	379.289	350	15	1.5
PTDP-6	50	520.711	350	15	1.5
PTDP-7	50	450	279.289	15	1.5
PTDP-8	50	450	420.711	15	1.5
PTDP-9	50	450	350	15	1.5

Fig.1. various transdermal patches of PXM

The study employed a central composite design with two factors (HPMC E50LV and HPMC E50LV) and nine combinations. The folding endurance (FE) and drug release at 24 hours (DR@24h) were the responses studied using Design Expert Software (Version 11). The relationships between the factors and responses were determined through statistical evaluation, including regression analysis.

The stepwise forward and backward elimination process was used in the regression analysis to identify significant factors or variables in the equation. Starting with an empty model in the stepwise forward elimination process, variables were added one by one based on their statistical significance (p-value < 0.05). In the stepwise backward elimination process, a full model with all potential variables was iteratively reduced by removing the least significant variables until only statistically significant variables remained (p-value < 0.05). This stepwise approach helped identify the most significant factors that influenced the dependent variables (FE and DR@24h) and improve the interpretability of the model by focusing on variables with a meaningful impact.

3.1. Compatibility studies:

FTIR analysis was performed to assess the compatibility of piroxicam with the polymers. PXM was mixed and triturated with dry KBr, and pellets were prepared for obtaining the infrared spectra. This analysis helps determine if there are any chemical interactions or changes in the functional groups of the drug and polymers when combined.

3.2. Physical appearance:

Visual inspection of the transdermal drug patches (PTDPs) was conducted to evaluate their color, clarity, flexibility, and smoothness. This examination provides an overall assessment of the PTDPs' appearance and quality.

Thickness measurements of the PTDPs were taken using a micrometer. Three different locations on each PTDP were measured to account for any variations. The average thickness value was calculated to assess the consistency and uniformity of the PTDPs.

3.3. Uniformity of weight:

Three PTDPs from each formulation were randomly selected, and the mean weight of six PTDPs from each batch was calculated. This evaluation ensures that the PTDPs have consistent weight, indicating uniformity in the manufacturing process.

3.4. Folding Endurance:

The folding endurance of a PTDP was determined by repeatedly folding it in the same spot until it broke. The number of times the PTDP could be pleated without breaking indicates its durability and flexibility.

3.5. Tensile strength:

A pulley system was used to measure the tensile strength of the PTDP. A PTDP was attached to adhesive tape at one end and subjected to increasing pulling force by adding weights. The maximum force the PTDP could withstand before breaking or deforming was measured. This evaluation assesses the PTDP's mechanical properties, including flexibility, durability, and resistance to stretching or tearing.

3.6. Moisture content:

PTDPs were kept in desiccators with CaCl2 at room temperature for 24 hours. The PTDPs' weight was measured at specified intervals until a constant weight was achieved. The moisture content was calculated using the initial and final weights of the PTDPs. This evaluation helps determine the PTDPs' moisture-absorbing capacity.

3.7. Assay:

A portion of the PTDP was cut, and phosphate-buffered saline was added to extract the drug. The solution was filtered, and the drug content was spectrophotometrically analyzed at 336 nm. This assay determines the amount of drug present in the PTDPs and ensures they meet the desired drug content specifications.

3.8. *In Vitro* Diffusion Study:

Franz diffusion cells were used to conduct in vitro diffusion studies. The PTDP was placed on a cellophane membrane, with a receptor compartment containing a phosphate buffer solution at pH 7.4. Samples were collected at predetermined intervals to analyze the drug content in the receptor fluid. This evaluation provides insights into the release and diffusion kinetics of the drug from the PTDP and its ability to deliver the drug effectively.

These evaluations assess various aspects of the PTDPs, including compatibility, physical appearance, uniformity, mechanical properties, moisture content, drug content, and drug release kinetics. They are important for ensuring the quality, performance, and consistency of the transdermal drug delivery systems containing piroxicam.

Results and discussion

The FTIR (Fourier-transform infrared spectroscopy) technique was used in this study to analyze the chemical and physical interactions between PXM (piroxicam) and the polymers used in the transdermal patch (PTDP). FTIR spectroscopy is a powerful analytical technique that provides information about the functional groups present in a sample based on their absorption of infrared light. Figure 2 in the study likely shows the IR spectra obtained from the analysis. This figure allows researchers to visualize the absorption peaks and patterns in the IR spectra of PXM and the polymers. By comparing these spectra, researchers can determine if there are any significant changes or interactions occurring between PXM and the polymers. The FTIR analysis helps in understanding the compatibility between the drug and the polymers used in the PTDP. If there are significant changes in the IR spectra or the appearance of new peaks, it suggests potential chemical interactions or complex formations between PXM and the polymers. Conversely, if the major peaks in the IR spectra remain unchanged, it indicates that there are no substantial physical interactions between PXM and the polymers. The results from the FTIR analysis contribute to the overall assessment of the compatibility of PXM with the polymers, providing valuable information for the development and formulation of the transdermal patch. The results of the FTIR analysis indicated that the major peaks in the IR spectra of the PXM-polymer mixture did not undergo any significant changes. This observation suggests that there were no substantial physical interactions between PXM and the polymers, namely HPMC E50LV and Eudragit RS 100. In addition to the FTIR analysis, various physical and chemical properties of the PTDP were evaluated to assess its overall quality.

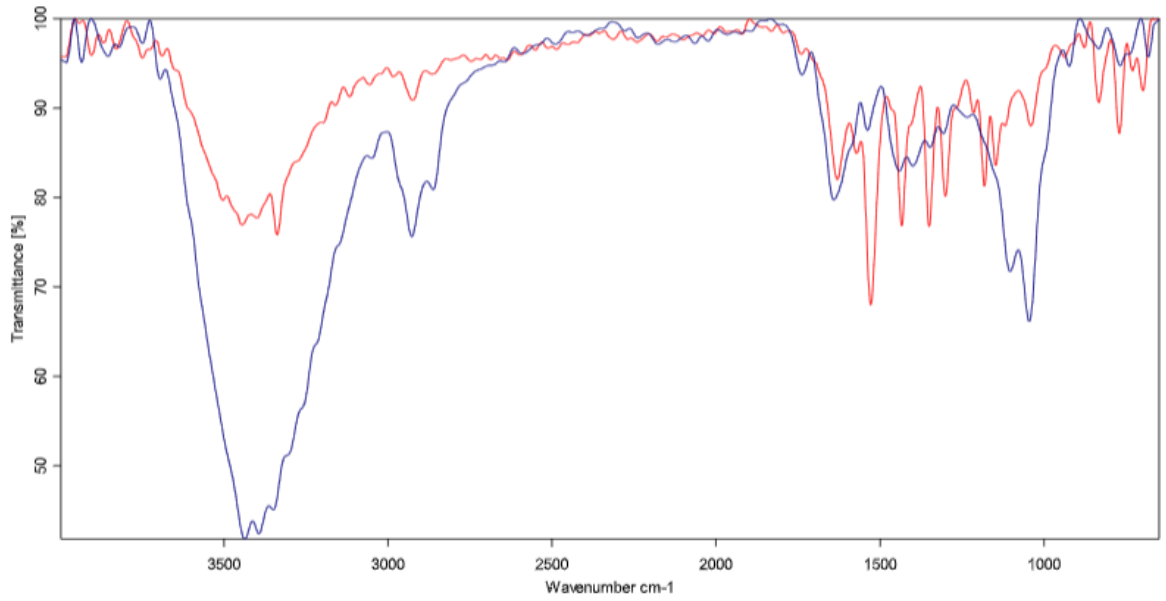

Fig.2. FTIR spectra of PXM and its excipients

These properties included appearance or visual inspection, thickness, weight uniformity, folding endurance (FE), moisture content, tensile strength, % elongation at break, and % drug content. Based on the evaluation of these properties, it was determined that the PTDP met the required standards and exhibited satisfactory characteristics. This implies that the PTDP had desirable physical attributes, such as appearance, thickness, weight distribution, and mechanical properties (tensile strength and elongation). Additionally, the PTDP demonstrated appropriate drug content, ensuring the intended dosage of PXM was delivered. Overall, the combination of FTIR analysis and the assessment of physical and chemical properties provided valuable information regarding the compatibility and quality of the PTDP formulation (Table 2, and Figure 3). The maximum DR@24h is shown by PTDP-1 and PTDP-5 PTDP. The PTDP also appears to fold best with the PTDP-8 and PTDP-9. Tensile strengths range between 0.452±0.01 and 0.482±0.01 mg/cm^2/h for all batches. The moisture content in the PTDP was within the limits. The responses, namely FE and DR@24h when placed in Design-Expert software and analyzed the fit summary (Table 3) and ANOVA details (Table 4) were produced.

Table 2: Physicochemical of PTDP

Formulation	Physical appearance	Thickness (mm)	Uniformity of weight (mg)	Folding endurance	Moisture content (%)	Tensile strength (mg/cm^2/h)	Assay (%)
PTDP-1	Good	45.25±1.26	250.63±6.3	125±5	4.6±0.01	0.452±0.01	95.30±2.35

PTDP-2	Very good	46.71±1.50	250.51±9.5	160±6	4.2±0.02	0.465±0.02	97.52±3.24
PTDP-3	Good	47.14±2.00	252.25±6.5	127±4	4.3±0.10	0.455±0.02	96.32±2.84
PTDP-4	Good	44.17±0.95	251.73±1.3	161±8	4.5±0.03	0.469±0.03	98.65±4.51
PTDP-5	Very good	45.02±0.68	272.29±5.2	124±5	4.6±0.06	0.468±0.01	96.51±3.62
PTDP-6	Good	44.99±0.52	260.71±7.4	165±6	4.4±0.08	0.469±0.02	97.84±2.25
PTDP-7	Good	45.87±0.84	279.28±8.2	145±2	4.1±0.09	0.478±0.02	98.62±3.81
PTDP-8	Very good	45.08±0.67	280.11±5.2	144±8	4.2±0.06	0.482±0.01	94.58±6.25
PTDP-9	Good	44.66±0.99	255.38±4.1	143±9	4.3±0.11	0.468±0.03	96.38±3.28

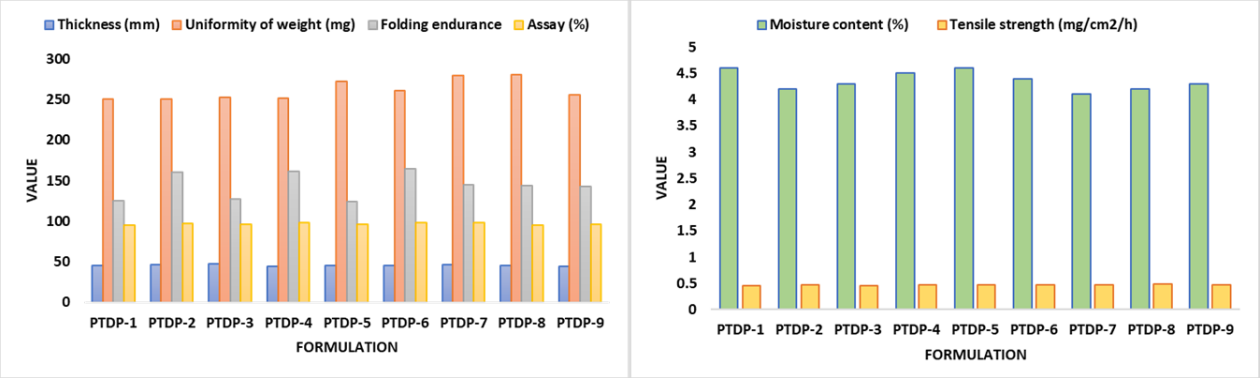

Fig. 3. Graphical depiction of the physicochemical assets of PTDP

Table 3: Fit Summary of the responses

Response 1: Folding Endurance			
Source	**Sequential p-value**	**Adjusted R^2**	**Predicted R^2**
Linear	**< 0.0001**	**0.9858**	**0.9743**
2FI	0.8187	0.9832	0.9543
Quadratic	0.9527	0.9729	
Cubic	0.3882	0.9877	
Response 2: DP@24h			
Linear	**0.0013**	**0.8560**	**0.8001**
2FI	0.9137	0.8276	0.7602
Quadratic	0.0889	0.9428	
Cubic	0.3642	0.9772	

Table 4: ANOVA for a Quadratic Model

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**

Response 1: Folding Endurance						
Model	2016.82	5	403.36	58.37	0.0035	significant
A-HPMC E50LV	2015.58	1	2015.58	291.65	0.0004	
B-Eudragit RS 100	0.3143	1	0.3143	0.0455	0.8448	
AB	0.2500	1	0.2500	0.0362	0.8613	
A^2	0.5568	1	0.5568	0.0806	0.7950	
B^2	0.5568	1	0.5568	0.0806	0.7950	
Residual	20.73	3	6.91			
Cor Total	2037.56	8				
Response 2: DP@24h						
Model	303.92	5	60.78	27.35	0.0105	significant
A-HPMC E50LV	276.05	1	276.05	124.21	0.0015	
B-Eudragit RS 100	0.9929	1	0.9929	0.4467	0.5517	
AB	0.0870	1	0.0870	0.0392	0.8558	
A^2	26.38	1	26.38	11.87	0.0411	
B^2	7.67	1	7.67	3.45	0.1602	
Residual	6.67	3	2.22			
Cor Total	310.59	8				

The combination of FTIR analysis and the assessment of physical and chemical properties provided valuable information regarding the compatibility and quality of the PTDP formulation. Here are some key findings based on the provided information:

PTDP-1 and PTDP-5 exhibited the highest drug release (DR) rates at 24 hours (Figure 4). This suggests that these specific batches of PTDP had formulations or characteristics that facilitated a faster release of the drug, possibly resulting in a quicker onset of therapeutic effects.

PTDP-8 and PTDP-9 demonstrated better folding endurance compared to other batches. This implies that these specific PTDP formulations were more resistant to repeated folding, indicating higher durability and flexibility.

The tensile strengths of all PTDP batches ranged between 0.452±0.01 and 0.482±0.01 $mg/cm^2/h$. This indicates that the PTDP formulations had consistent tensile strength values within this range. Tensile strength is a measure of a material's ability to resist breaking under

tension, and the narrow range suggests that the PTDP batches had comparable mechanical strength.

The moisture content in the PTDP was within acceptable limits. This indicates that the PTDP formulations maintained the desired moisture levels, which is important for the stability and preservation of the patch's properties during storage and use.

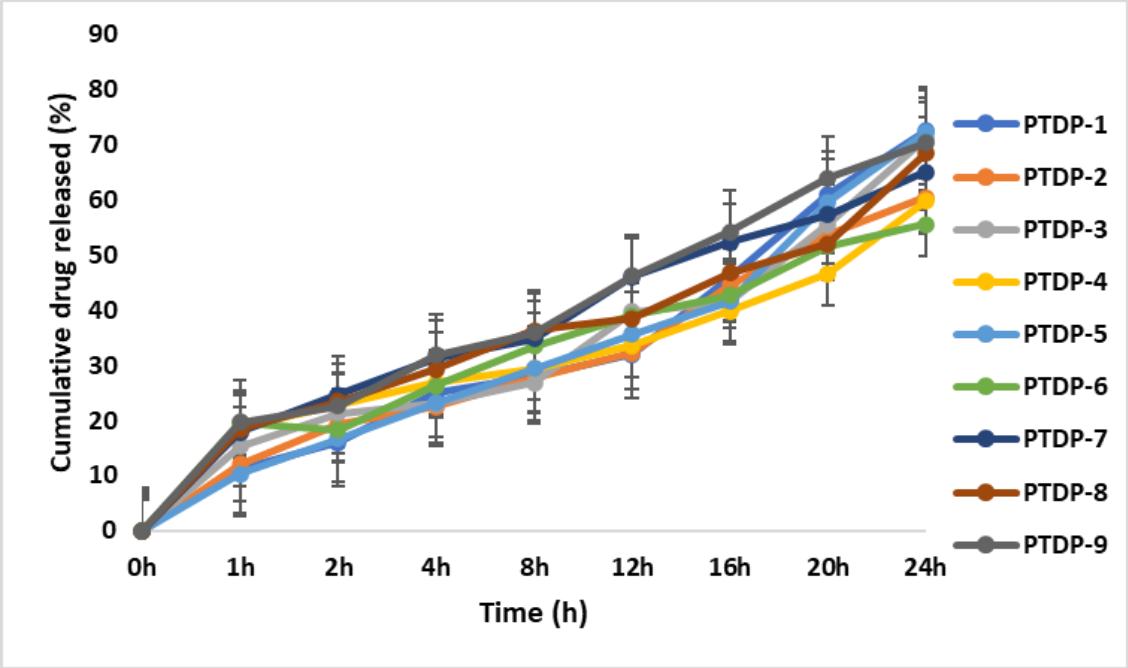

Fig.4: *In vitro* PXM permeation graph till 24 h

The responses, namely Folding Endurance (FE) and Drug Release at 24 hours (DR@24h), were analyzed using Design-Expert software. The fit summary (Table 3) and ANOVA details (Table 4) provide information about the statistical model and the significance of the model terms, including factors and interactions. These analyses help determine the relationships between the factors and the responses, assess the overall significance of the model, and guide decision-making in optimizing the PTDP formulation.

Overall, the combination of FTIR analysis, physical and chemical property assessments, and statistical analysis using Design-Expert software provides comprehensive insights into the compatibility, quality, and performance of the PTDP formulation. These findings contribute to understanding the factors influencing key properties such as drug release, folding

endurance, tensile strength, and moisture content, enabling optimization and quality control of the transdermal patch.

The F-value is a statistical measure used to assess the overall significance of the model. It indicates the ratio of the mean square variation explained by the model to the mean square variation not explained by the model. A high F-value suggests that the model is significant and that the observed variations in the response variables are not due to random chance. In this case, an F-value of 58.37 suggests that the model is statistically significant.

The P-value, on the other hand, is used to determine the significance of individual model terms, such as factors or interactions. It represents the probability of obtaining the observed results if the null hypothesis (no effect) is true. A P-value below a certain significance level (often 0.05) indicates that the term is statistically significant and has a significant impact on the response variable. In contrast, a P-value above the significance level suggests that the term is not statistically significant.

By examining the P-values associated with each term in the statistical model, researchers can identify which factors or interactions are significant contributors to the variation in the response variables. This information helps in understanding the relationships between the factors and the response variables and can guide decisions related to model refinement or identifying important factors for optimization.

In summary, the F-value and P-values are essential statistical measures used to determine the significance of the model as a whole and individual model term, respectively. They provide insights into the reliability and importance of the statistical relationships in the analyzed model.

The F-value of 58.37 indicates that the overall model is significant, with a low probability (0.35%) of obtaining such a large F-value by chance alone. This suggests that the observed results are unlikely to be due to random fluctuations or noise.

Regarding the assessment of individual model terms using P-values, states that a P-value below 0.05 is generally considered significant, indicating that the term has a significant impact on the model. On the other hand, a P-value above 0.1 suggests that the model term is not significant.

Overall, the significance of the model and its terms, as determined by the F-value and P-values, helps in understanding the statistical significance of the model's relationships and can guide decisions regarding model reduction if there are many insignificant terms.

$FE = +143.00 + 15.87A + 0.1982B - 0.2500AB + 0.4375\ A^2 + 0.4375B^2$

When the equation is expressed in terms of coded factors, where high levels are represented as +1 and low levels as -1, researchers can analyze the coefficients of the factors to assess their influence on the response variable. Positive coefficients indicate that an increase in the factor level leads to an increase in the response, while negative coefficients suggest that an increase in the factor level leads to a decrease in the response. The magnitude of the coefficients provides insights into the strength of the relationship between the factors and the response variable. Larger coefficients indicate a stronger impact, while smaller coefficients suggest a weaker influence.

By comparing the coefficients in the coded equation, researchers can gain a better understanding of how different factors contribute to the response variable. This analysis helps in making predictions about the response based on specific factor levels and provides insights into the relationships between the factors and the response variable.

The coded equation and coefficients to assess the impact of factors and make predictions about the response variable.

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

Based on the information provided, it seems that the equation based on coded factors allows for predictions about the response variable based on specific levels of each factor. High levels of factors are represented as +1, and low levels are represented as -1.

The coefficients of the factors in the coded equation can be compared to determine the relative impact of each factor on the response variable. Positive coefficients indicate that an increase in the factor level (from low to high) leads to an increase in the response, while negative coefficients suggest that an increase in the factor level leads to a decrease in the response.

The graphs in Figures 5A and 5D show that the responses of FE and DR@24h were linear, indicating a consistent relationship between the factors and the responses. The close correlation between the residual vs. predicted values (Figures 5B and 5E) suggests that the model's predictions are accurate.

Figures 5C and 5F indicate that the cooking distance (the difference between the observed and predicted values) for FE and DR@24h is below the red line, which suggests that the model fits well with the actual data for these responses.

Figures 5G and 5H, as well as figures 5I and 5J, display 2D and 3D response surface plots, respectively. These plots illustrate the relationship between the factors (HPMC E50LV and Eudragit RS 100) and the responses (FE and DR@24h). By analyzing these plots, it is possible to understand how changes in the levels of HPMC E50LV and Eudragit RS 100 affect the folding endurance and drug release at 24 hours.

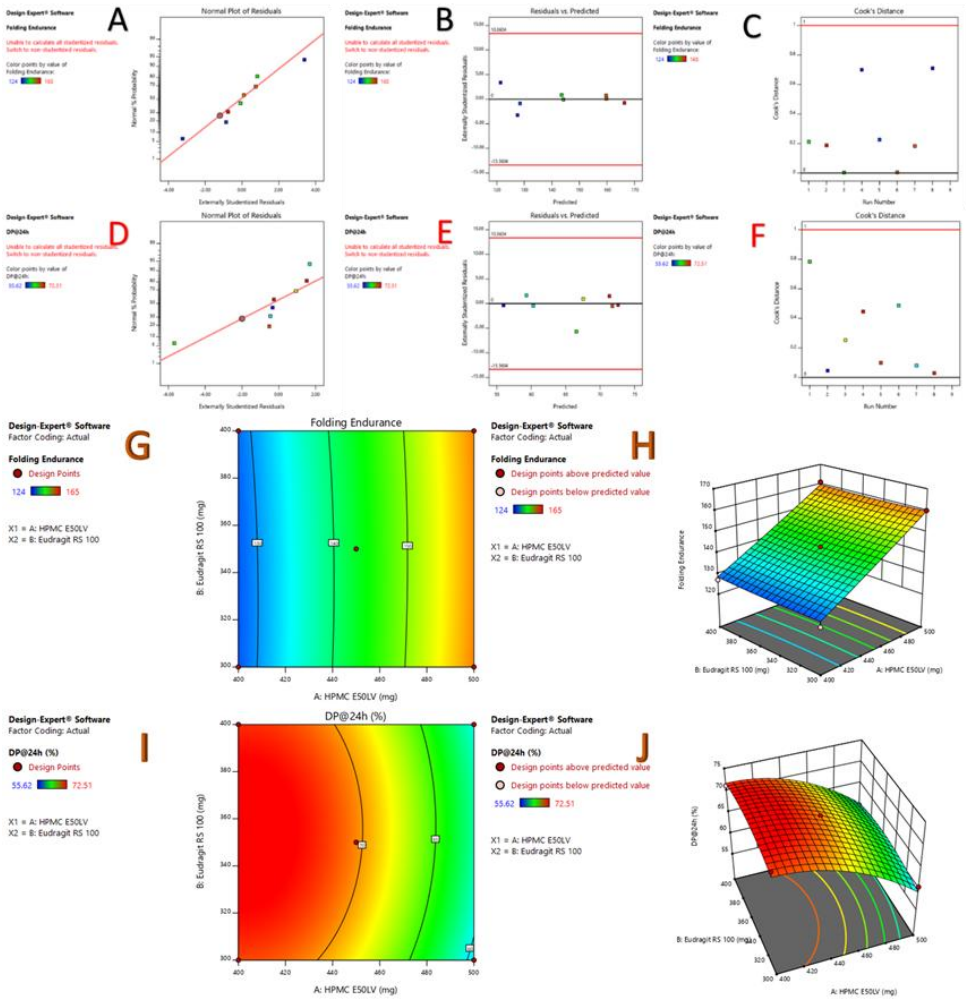

Fig.5. Normal (A&D), residual. vs. predicted (B&E), Cooks distance (C&F) and Response surface plots (G, H, I&J) showing the effect of HPMC E50LV and Eudragit RS 100

Overall, these visualizations and analysis provide insights into the effects of the factors on the responses and help in understanding the relationship between the formulation factors and the desired properties of the PTDP.

Conclusion

Based on the information provided, it appears that HPMC E50LV (400 mg) and Eudragit RS 100 (300 mg), along with glycerin as a plasticizer, have shown promise as a transdermal drug delivery system for controlled release of piroxicam from matrix-type transdermal patches. The combination of HPMC E50LV and Eudragit RS 100 likely provides the necessary properties for the transdermal patch, such as controlled drug release and matrix stability. Glycerin, as a plasticizer, may contribute to the flexibility and pliability of the patch. This formulation has likely undergone extensive evaluation, including physical and chemical characterization, as well as in vitro and potentially in vivo studies, to determine its effectiveness and safety for transdermal drug delivery. However, it is important to note that without access to the specific study or more detailed information, it is not possible to provide a comprehensive analysis or evaluation of the mentioned transdermal drug delivery system.

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