ijlpr 2023; doi 10.22376/ijlpr.2023.13.6.P366-P377

International Journal of Life science and Pharma Research

ISSN 2250-0480

Research Article

Anti-Allergic Transdermal Patches of Chlorpheniramine Maleate

Enhancing Anti-Allergic Transdermal Patches Through Box-Behnken Design Approach with Chlorpheniramine Maleate

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Abstract: This research focuses on developing transdermal patches incorporating chlorpheniramine maleate (CPM), an anti-allergic medication. Transdermal patches offer a convenient and effective way to administer drugs, and CPM's application in this context holds promise for improved patient care. The primary aim of this study was to utilize the Box-Behnken design to formulate transdermal patches containing CPM. These patches were developed through a solvent dispersion technique, with key ingredients including HPMC (a polymer), PEG (a plasticizer), ethanol, and a permeation enhancer. The overarching goal was to assess the impact of polymer type, permeation enhancer, and sonication time on patch formulation and performance. To achieve our aim, we conducted several tests, including folding endurance, drug content, thickness, entrapment efficiency, in vitro moisture uptake, permeation analysis, and in vitro experiments. These specific objectives allowed us to evaluate the quality and effectiveness of the transdermal patches comprehensively. In our methodology, HPMC was employed as the polymer, and PEG served as the plasticizer. The Box-Behnken design facilitated kinetic assessments to study drug release from the patches. We systematically varied the HPMC, PEG, and ethanol concentrations and the sonication time to optimize patch formulation. The outcomes of our study indicated that all formulated patches met the specified criteria for quality and performance. Folding endurance was found to follow the formula $+178.00 + 5.37A + 13.25B + 1.13C - 1.75AB + 0.0000AC + 0.2500BC + 4.25A^2 + 8.50B^2 + 2.75C^2$, while permeation at 24 hours exhibited the equation $+73.00 + 2.12A + 6.37B + 0.7500C - 0.5000AB - 0.2500AC - 0.2500BC + 1.00A^2 + 0.0000B^2 + 1.25C^2$. These findings underscore the successful development of transdermal patches containing CPM and shed light on the critical factors influencing patch formulation. In summary, this investigation accomplished the development of transdermal patches incorporating CPM and elucidated the influence of polymer type, permeation enhancer, and sonication time on the formulation process. These findings contribute to advancing transdermal drug delivery systems and offer potential benefits for patients receiving anti-allergic medication.

Keywords: Chlorpheniramine maleate, Design, In vitro studies, Permeation studies, Transdermal patch.

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Received On 21 August 2023
Revised On 12 September 2023
Accepted On 17 October 2023
Published On 1 November 2023

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Hindustan Abdul Ahad, Siriguppa Dheeraj and Haranath Chinthaginjala , Enhancing Anti-Allergic Transdermal Patches Through Box-Behnken Design Approach with Chlorpheniramine Maleate.(2023).Int. J. Life Sci. Pharma Res.13(6), P366-P377 http://dx.doi.org/10.22376/ijlpr.2023.13.6.P366-P377

1. INTRODUCTION

Transdermal drug delivery systems (TDDS) represent an innovative approach to medication administration. Science offers many advantages over traditional routes, such as oral or injectable. These systems are designed to optimize the absorption of drugs through the skin, enhancing systemic circulation while minimizing drug-related gastrointestinal issues and poor absorption. One significant benefit of transdermal drug delivery is its ability to bypass first-pass metabolism, leading to increased drug efficacy. Moreover, this method of drug administration results in lower peak plasma levels, reducing the likelihood of adverse side effects. Prior research has underscored the potential of transdermal drug delivery systems in improving drug delivery efficiency and patient compliance. However, limited work has been conducted on developing a TDDS for chlorpheniramine maleate (CPM), an antihistamine used to treat allergies. CPM has unique characteristics, including a hydrophobic ring structure and a hydrophilic side chain with a charged cationic amino group, classifying it as a cationic amphiphilic amine drug[1]. Transdermal administration can improve patient compliance and bypass first-pass metabolism, resulting in higher efficacy than injectable and oral routes[2]. The gap in previous research lies in the need for more investigations into the TDDS of CPM using specific variables and their interactions, such as HPMC polymer, PEG as a plasticizer, and sonication time. Moreover, no prior studies have examined the impact of these variables on folding endurance and entrapment efficiency as dependent variables[3]. Given the therapeutic significance of CPM in managing allergies and the potential benefits of transdermal delivery, there is a clear need for a systematic study that explores the development of a TDDS for CPM. This research aims to bridge the existing gap in knowledge and offer insights into optimizing the transdermal delivery of CPM for enhanced therapeutic outcomes[4]. This study is unique in its approach, as it employs a Box-Behnken Design (BBD) to systematically investigate the impact of HPMC polymer, PEG as a plasticizer, and sonication time on folding endurance and entrapment efficiency in the context of CPM TDDS. Design Expert software allows for a rigorous examination of these factors and their interactions, paving the way for more efficient and effective transdermal drug delivery systems[5]. This method of administration avoids the gastrointestinal tract and keeps plasma levels steady over a lengthy period[6]. Alkylamine derivative chlorpheniramine maleate (CPM) is an antihistamine that acts as an antagonist of the H1 receptor and is used to treat allergies. They limit but do not stop the histamine-induced reactions. The majority of histamine's pharmacological effects, such as urticaria and pruritus, are countered by CPM[7]. CPM, similar to other antihistamines, has a half-life of 21 to 24 hours and can cause mucosa dryness by blocking muscarinic receptors' response to acetylcholine. The unique characteristics of CPM include a hydrophobic ring structure and a hydrophilic side chain with a charged cationic amino group, which classify it as a cationic amphiphilic amine drug (CAD)[8]. The primary objective of this study is to develop and optimize a transdermal drug delivery system (TDDS) for Chlorpheniramine (CPM) using a Box-Behnken Design (BBD) approach. This entails formulating transdermal patches containing CPM with varying concentrations of HPMC polymer, utilizing PEG as a plasticizer, and exploring different sonication times. Additionally, the study aims to assess the mechanical properties of these patches through folding endurance tests and determine the entrapment efficiency of CPM to gauge drug retention within the patches. Furthermore, the investigation seeks to analyze how variations in HPMC polymer concentration, PEG content, and sonication time influence folding endurance and entrapment efficiency. Ultimately, the goal is to optimize the TDDS formulation, identifying the ideal combination of parameters that maximize folding endurance and entrapment efficiency while ensuring the stability of CPM, potentially offering a more efficient and convenient method of administering this medication through transdermal patches. This study seeks to contribute valuable insights into developing transdermal drug delivery systems, particularly for CPM, and enhance our understanding of the factors influencing patch properties and drug retention. Ultimately, the research aims to improve the efficiency and effectiveness of CPM delivery, benefiting patients with allergies and potentially serving as a model for other drugs with similar characteristics. Design Expert software was adopted to design the formulations as per BBD[9].

2. MATERIALS AND METHODS

The CPM product was acquired as a complimentary sample from Dr. Reddy's. HPMC, PEG, and Ethanol were purchased from Loba Chemie Pvt Ltd, Mumbai. Double distilled water (from the lab unit) was used whenever desirable.

2.1. Methods

The transdermal patch was created using the solvent dispersion technique. The fusion of ethanol and CPM was vortexed for 10 min before adding HPMC. A clear solution should have resulted from this process. Then, continued sonication while adding PEG to the solution above. The homogenous solution that had been produced was placed onto a slab greased with glycerine and allowed to air dry. Dry patches were removed after 24 h and kept in a desiccator for future research (Table 1).

Table 1. Experimental plan for chlorpheniramine malate

Formulation	CPM(mg)	Independent variables			Dependent variables		Ethanol (ml)
		HPMC (mg)	PEG (ml)	Sonication time (min)	Permeation (%)	Folding endurance	
F1	0.1	2	1.00	15	80.00	172	10
F2	0.1	8	1.00	15	91.20	185	10
F3	0.1	2	1.50	15	81.25	200	10
F4	0.1	8	1.50	15	93.40	206	10
F5	0.1	2	1.25	15	83.30	178	10
F6	0.1	8	1.25	15	95.60	190	10
F7	0.1	2	1.25	15	84.90	180	10
F8	0.1	8	1.25	15	97.00	192	10
F9	0.1	5	1.50	10	85.20	174	10

F10	0.1	5	1.50	10	86.30	202	10
F11	0.1	5	1.00	20	87.80	176	10
F12	0.1	5	1.50	20	88.50	205	10
F13	0.1	5	1.25	15	90.50	178	10

3. STATISTICAL INVESTIGATIONAL DESIGN

To optimize the formulation factors and variables for the transdermal film of CPM, A statistical design known as the Box-Behnken design, which incorporates three factors and three levels, was utilized for the experiment. The Design-Expert 11.1.0.1 software, developed by Stat-Ease Inc. located in Minneapolis, MN, USA, was employed for the analysis. The experimental design included three independent variables: the ratio of HPMC as film-forming polymers, the concentration of PEG as a plasticizer, and two dependent variables, folding endurance and EE. The coding information and values for the independent variables are provided in text[11]. The response variable, denoted as R, was analyzed concerning the independent variables A, B, and C, corresponding to the concentration of plasticizer, permeation enhancer, and polymer (HPMC). The regression coefficient is represented by 0. The experiment was randomized to account for the effects of unpredictable exogenous factors on the observed responses. The interactions between the independent variables AB, AC, and BC were considered to explain the variations in the response. The resulting polynomial equation was used to model the relationship between the independent and dependent variables.

4. EVALUATION TESTS

The prepared patches were assessed for the following constraints: [12-14].

4.1. Weight variation

The films were reduced to the requisite 1.76 cm2 size. They were weighed three times on a digital balance, and the average value for each combination was determined.

4.2. Thickness

Vernier calipers were used to measure patch thickness at various locations. Standard deviations and average values were calculated.

4.3. Drug content

The appropriate patch size was soaked in phosphate buffer (pH 7.4), sonicated at 25°C for 30 min, and then centrifuged for 15 min in a volumetric flask of 10 mL. The solutions were filtered using 0.45 µm filters, and their spectrophotometric analysis was performed.

4.4. Folding endurance

A strip of a particular area was evenly cut, folded multiple times in the same spot, and then torn. The number of folds that could be made with the film in the same location without breaking determined its folding endurance.

4.5. Flatness

Longitudinal strips were obtained from the prepared patches, and the thickness of each strip was measured. The variation in thickness (vertical length) was also measured to account for non-uniformity in flatness. A constriction of 0% was considered 100% flatness when determining the flatness of the strips by measuring their unevenness. (e.q.1)

$$\%\ Constriction = \frac{Average\ thickness - thickness\ at\ sample\ point}{Average\ thickness} X100 \text{--- (1)}$$

4.6. Tensile strength

It was measured using equipment for assessing universal strength. Maximum force was applied to the film, in this case, at any point along its length up to the film broke. The tensile strength was determined by dividing the greatest tensile force exerted at the break by the fractional area of the film. Using the following formula, the tensile strength was calculated.

4.7. Moisture content

The reweighed films were aced in a desiccator with fused calcium chloride and left there for 24 hours at room temperature. Reweighing the films after 24 h yielded the % moisture content (e.q.2).

$$\%moistu\text{- (2)}$$

4.8. Percent elongation

An elongation testing apparatus was employed for testing percent elongation by using eq. 3.

% elongation = (L1-L2) L1×100--- (3)

L1 and L2 are the original and final lengths of the film, respectively.

4.9. Uniformity of drug content

Ten patches were selected to assess their content uniformity. A transdermal patch passes the content uniformity test if nine out of the ten patches contain material within 85% to 110% of the specified value, while one patch has content between 75% and 125%. However, if three patches contain a medication content of 75% to 125%, an additional 20 patches will be

required. These 20 patches will undergo analysis, and their variation should be within the 85% to 110% range to pass the content uniformity test.

4.10. In vitro drug release

The following procedure was used to test the dissolution of selected patches using a USP class II dissolution test device. The patches were attached to a stainless-steel disc assembly. The disc assembly's and paddle's surfaces were separated by 252 mm. A cover was placed over the vessel to stop evaporation. The entire assembly was submerged in 900 ml of pH 7.4 phosphate buffer at 32°C. The rotational speed was set to 100 rpm. Samples were taken, and a new medium was added. Once the solution was filtered, the absorbance at 252 nm was measured. Plots were made showing drug release % and time.

4.11. Permeation studies

The produced patches were used in *invitro* permeation tests using Franz diffusion cells. A cellophane membrane is installed in the diffusion cell, which has a cross-sectional area of 3.14 cm^2. A strong membrane seal separated the donor compartment from the receptor chamber. The patch was then retained on the membrane's upper surface[15]. A 14.5 ml of pH 7.4 phosphate buffer was placed within the receptor compartment. A magnet was used to agitate the mixture at a speed of 60 rpm while keeping the temperature at 32°C. 1 ml of the sample was taken at regular intervals, and a fresh buffer solution was added. Then, the samples were examined with a UV spectrophotometer at 252 nm.

5. RESULTS

5.1. Results of physicochemical constraints

The drug was carefully kept over the sample holder for scanning during the FTIR analysis (Figure 1) to identify the excipient compatibility with the drug and found that the drugs and excipients are compatible with each other.

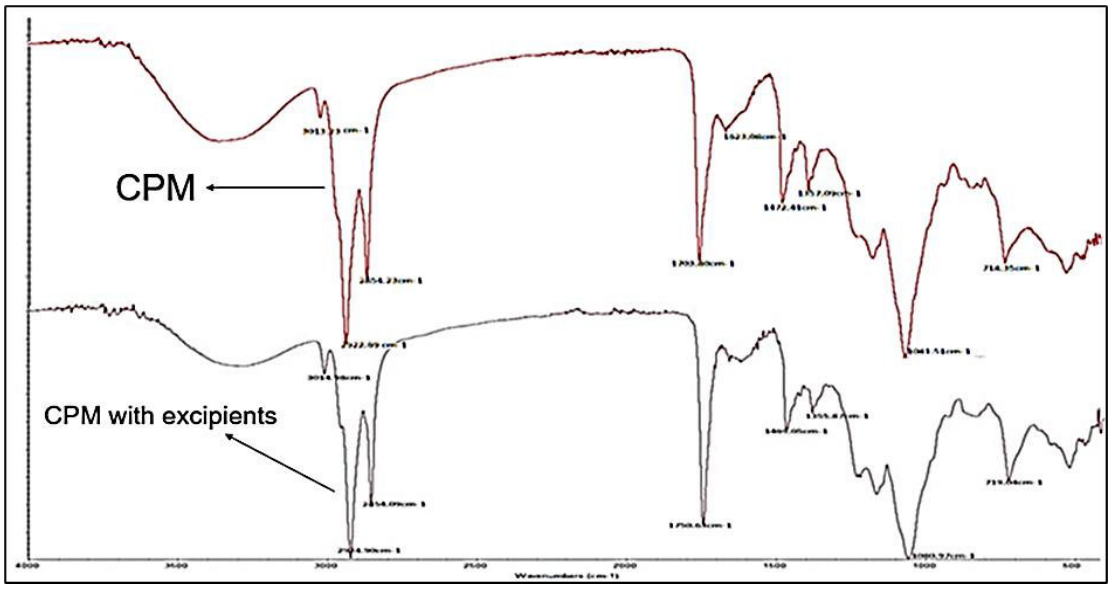


Fig.1. FTIR spectrum of CPM and its blend

Recently, there has been a lot of interest in oral site-specific drug delivery systems for the local treatment of several intestinal illnesses and for enhancing systemic absorption of medications that are unreliable in the stomach. However, the milieu in the digestive tract and different absorption methods often present challenges for formulation scientists when developing and perfecting oral drug administration. However, the HPMC, PEG, and sonication time were chosen for further formulations based on producing a uniform, smooth, transparent, and flexible film. A solvent dispersion technique was used to create transdermal patches of CPM to obtain a regulated release and enhanced bioavailability of the medicinal substance. The thickness of each drug-loaded transdermal patch was discovered to be rather consistent. The thickness range for each transdermal patch was between 0.385±0.04 and 0.414±0.03, and F5 had the batch's highest thickness, whereas F1's lowest thickness was found. These findings showed that the polymer's solubility and concentration impact the polymer's thickness. The patch's thickness would increase as concentration and solubility decreased. It implies that using the right polymer is necessary for creating a patch with the right thickness, which can delay the release of the medication from the patch. The weight of the transdermal batches ranges from 86.3±2.08 to 98.3±2.51 mg, while the drug content was found to be between 98.97±2.38 and 100.07±2.51 CPM in all of them. The drug content of every formulation showed that the method used to make the study's patches could produce patches with consistent drug content and few patch variabilities. The SD value demonstrated that the patches were uniform across all tests. The batches' folding endurance was assessed. Between 172±1.9 and 205±1.5, it fluctuates. The prepared patches' capacity to bear mechanical pressure and maintain acceptable flexibility was also demonstrated by the 185-folding endurance. Compared to formulations constructed of PVP, HPMC formulations were shown to have the highest value of folding endurance. Concentrations of polymers also play a significant effect in folding endurance (Table 2).

Table 2. Thickness, folding endurance, drug content, and weight of patches.

Formulation	Thickness (mm)	Folding endurance	Drug content (%)	Weight (mg)
F1	0.385±0.04	172±1.9	99.08±5.28	89.3±2.13
F2	0.394±0.05	185±1.8	99.89±1.61	88.6±3.84
F3	0.401±0.09	200±1.4	100.04±2.35	86.3±2.08
F4	0.404±0.06	206±1.1	99.99±2.66	91.2±3.70
F5	0.414±0.03	178±1.3	99.86±3.25	90.3±1.67
F6	0.410±0.05	190±0.7	99.62±1.28	91.3±2.84
F7	0.389±0.05	180±0.8	99.94±4.02	89.3±2.01
F8	0.392±0.05	192±3.5	99.85±2.85	86.8±4.61
F9	0.386±0.05	174±2.4	98.97±2.38	89.8±2.85
F10	0.391±0.05	202±0.9	99.86±1.54	92.2±1.64
F11	0.397±0.05	176±1.6	99.67±3.35	94.3±2.41
F12	0.391±0.05	205±1.5	99.87±1.52	98.3±2.51
F13	0.402±0.05	178±2.3	100.07±2.51	89.8±1.25

Values in mean ± SD; n=3

The transdermal patches' flatness percentage ranged from 97.13±2.13 to 99.67±2.52%. The amount of moisture absorbed by all films increased from 8.16±0.37 to10.85±0.28%. The polymer's hygroscopic properties may be due to the increased moisture absorption. All of the patch showed weight gain over time. Testing revealed that the surface pH of the patches' formulations ranged uniformly from 5.09±0.16 to 5.84±0.17. For the formulations F1 to F13, the % elongation ranged from 39.30±2.61 to 68.97±2.36%, with formulation F5 exhibiting the highest % elongation (Table 3).

Table 3. Physical assets of prepared patches.

Formulation	Surface pH	% Flatness	% Elongation	Moisture content (%)	Moisture uptake (%)
F1	5.51±0.08	98.67±2.08	49.49±2.89	7.58±0.81	8.85±0.05
F2	5.50±0.05	97.35±1.45	47.85±3.64	7.09±0.12	9.16±0.82
F3	5.65±0.09	99.67±2.52	59.33±1.44	7.78±0.51	8.16±0.37
F4	5.77±0.10	99.67±1.15	63.67±1.44	9.97±0.34	10.85±0.28
F5	5.55±0.19	98.29±2.49	68.97±2.36	7.41±0.56	8.49±0.17
F6	5.27±0.07	97.43±0.46	65.46±1.30	7.07±0.65	9.65±0.03
F7	5.09±0.16	97.13±2.13	39.30±2.61	8.94±0.84	8.23±0.04
F8	5.29±0.15	99.89±0.76	48.33±1.95	9.62±0.11	8.96±0.67
F9	5.84±0.17	98.53±2.19	56.53±1.53	9.85±0.08	10.20±0.54
F10	5.29±0.36	98.81±0.56	59.49±1.49	7.95±0.66	constraints
F11	5.57±0.81	99.46±2.43	65.32±2.76	7.88±0.08	8.63±0.32
F12	5.34±0.09	98.68±0.88	59.46±2.38	9.05±0.13	9.62±0.23
F13	5.44±0.15	99.51±2.16	60.16±1.92	7.77±0.13	9.09±0.51

Values in mean±SD; n=3

In vitro drug release

The patches were attached to a stainless-steel disc assembly. The disc assemblies and paddles were separated by 252 mm. A cover was placed over the vessel to stop evaporation. The entire assembly was submerged in 900ml of pH 7.4 phosphate buffer at 32°C. The rotational speed was set to 100 rpm. Samples were taken, and a new medium was added. Once the solution was filtered, the absorbance at 252 nm was measured. Plots were made showing drug release % and time. *In vitro,* the dissolution of CPM patches was as per Figure 2.

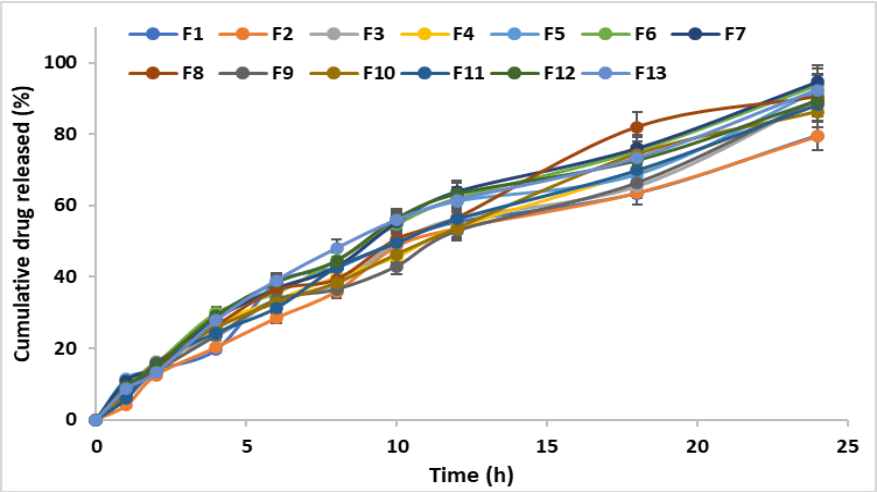


Fig.2. *In vitro* drug dissolution profile of the patches

The data from the in vitro drug release was analyzed using a variety of release kinetics models, including first order, zero order, Higuchi's equation, and Korsmeyer Peppa's equation. It was discovered that the model with the highest correlation (R^2) value best described the drug release kinetics of the patches based on the highest correlation (R^2) value (Table 4).

Table 4. Kinetic details of drug release data from the patches

Formulation	Zero order (r^2)	The first order (r^2)	Higuchi kinetics (r^2)	Kores Meyers peppas (r^2)
F1	0.8151	0.9804	0.9326	0.9010
F2	0.8105	0.9751	0.9524	0.8789
F3	0.8052	0.9754	0.9364	0.8956
F4	0.8216	0.9794	0.9485	0.8858
F5	0.7968	0.9958	0.9101	0.9041
F6	0.7858	0.9884	0.9084	0.9069
F7	0.7957	0.9854	0.9017	0.9103
F8	0.8152	0.9758	0.9529	0.9052
F9	0.8051	0.9756	0.9347	0.8998
F10	0.8212	0.9915	0.9390	0.8974
F11	0.8003	0.9802	0.9357	0.8901
F12	0.7985	0.9732	0.9083	0.9088
F13	0.7775	0.9807	0.9100	0.9011

The permeation profile of the patches was as per Figure 3.

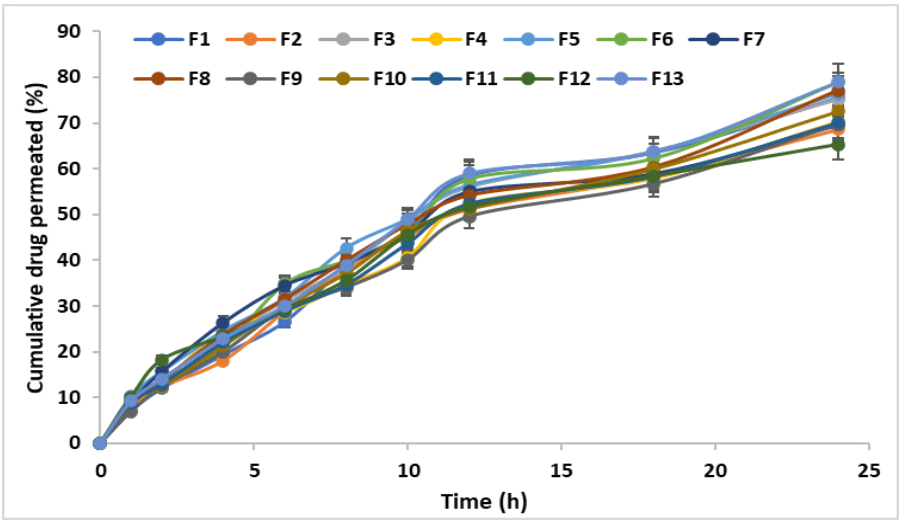


Fig.3. Permeation of CPM from the patches

5.2. QBD employed in patch

After analyzing the data and placing it in the Design Expert software, it suggested and fitted the quadratic and linear models (Table 5).

Table 5. Adjusted and predicted values for the responses studied.

Response 1: FE				
Source	**Sequential p-value**	**Adjusted R^2**	**Predicted R^2**	
Linear	**< 0.0001**	**0.8597**	**0.8189**	**Suggested**
2FI	0.9336	0.8032	0.6686	
Quadratic	**0.0258**	**0.9755**		**Suggested**
Cubic				
Response 2: Permeation @24h				
Linear	**< 0.0001**	**0.9738**	**0.9620**	**Suggested**
2FI	0.6870	0.9688	0.9354	
Quadratic	**0.0149**	**0.9973**		**Suggested**
Cubic				

The ANOVA for the Quadratic model was significant (Table 6).

Table 6. The ANOVA for Quadratic model.

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	1827.98	9	203.11	54.16	0.0037	significant
A-HPMC	231.12	1	231.12	61.63	0.0043	
B-PEG	1404.50	1	1404.50	374.53	0.0003	
C-SOT	10.13	1	10.13	2.70	0.1989	
AB	12.25	1	12.25	3.27	0.1684	
AC	0.0000	1	0.0000	0.0000	1.0000	
BC	0.2500	1	0.2500	0.0667	0.8130	
A^2	41.29	1	41.29	11.01	0.0451	
B^2	165.14	1	165.14	44.04	0.0070	
C^2	17.29	1	17.29	4.61	0.1211	
Residual	11.25	3	3.75			
Cor Total	1839.23	12				
Response 2: Permeation at 24h						
Model	372.83	9	41.43	497.10	0.0001	significant
A-HPMC	36.12	1	36.12	433.50	0.0002	
B-PEG	325.12	1	325.12	3901.50	< 0.0001	
C-SOT	4.50	1	4.50	54.00	0.0052	
AB	1.0000	1	1.0000	12.00	0.0405	
AC	0.2500	1	0.2500	3.00	0.1817	
BC	0.2500	1	0.2500	3.00	0.1817	
A^2	2.29	1	2.29	27.43	0.0135	
B^2	0.0000	1	0.0000	0.0000	1.0000	
C^2	3.57	1	3.57	42.86	0.0072	
Residual	0.2500	3	0.0833			
Cor Total	373.08	12				

The information provided suggests that the statistical model has been evaluated using the F-value and p-values of its terms. The F-value, which tests the overall significance of the model, is significant at a value of 54.16, indicating that the model can explain the variation in the response variable well. Additionally, the p-values of individual terms reveal that A, B, A^2, and B^2 are significant, indicating that these variables are important for explaining the variation in the response variable. However, any p-values greater than 0.1 would suggest that the corresponding model terms are insignificant and could be removed to improve the model's fit. It is important to note, however, that caution should be exercised when removing insignificant terms, as overly reducing the model's complexity could lead to underfitting the data and poorer performance on new data. Thus, it is essential to balance model simplicity and its ability to capture the important relationships in the data. According to the provided information, the statistical model has been evaluated using the F-value and p-values of its terms. The F-value of 497.10 indicates that the model is significant and can explain the variation in the response variable. The probability of this F-value occurring due to noise is only 0.01%, further supporting the significance of the model. In addition, the p-values of individual terms show that A, B, C, AB, A^2, and C^2 are significant terms in the model. These variables play an important role in explaining the variation in the response variable. However, any p-values greater than 0.1000 indicate that the corresponding model terms are insignificant and could be removed from the model. If there are many insignificant

model terms (not counting those required to support hierarchy), reducing the model by removing them may improve its fit. It's important to note that removing too many insignificant terms could lead to underfitting the data and poor performance on new data. Therefore, careful consideration should be given to balancing the model's simplicity with its ability to capture the important relationships in the data. When the normal plot of residuals (Fig.4.A) was obtained from normal % probability towards externally studentized residuals represents linearity, whereas residual vs. run (Fig.4.B) that was plotted from externally studentized residuals vs. run number represents the values were nearer to the midline. The Cook's distance (Fig.4.C) for the run numbers lying below 1 and the predicted vs. actuals plot (Fig.4.D) was linear, indicating the significance of the values obtained from the independent variables.

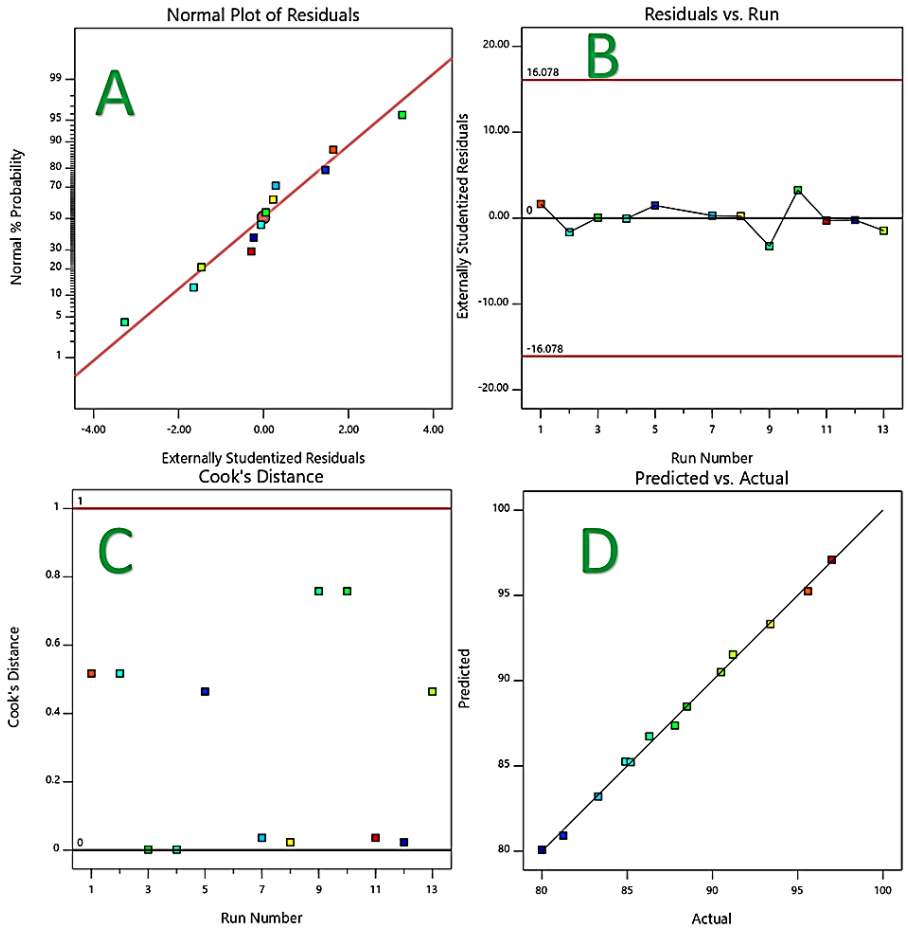
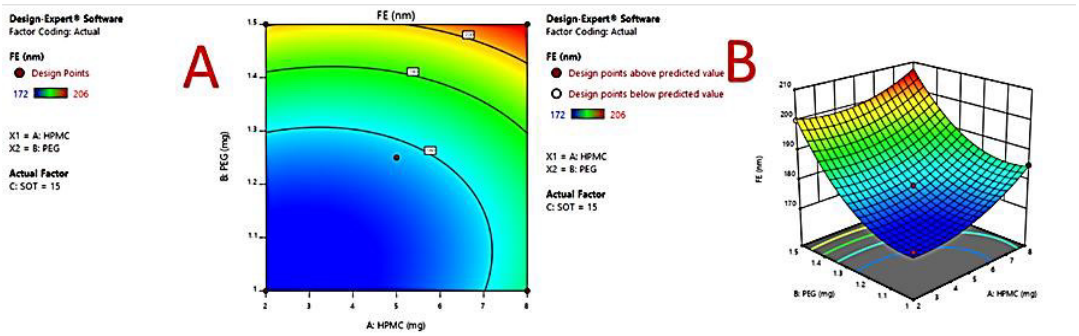


Fig.4. A) Normal plot of residuals B) Residual vs. run C) Cook's distance D) Predicted vs. actual for the independent variables.



The final equation in terms of coded factors is as follows.

$$\mathbf{FE} = +178.00 +5.37\ A +13.25\ B +1.13C -1.75\ AB +0.0000\ AC +0.2500\ BC +4.25\ A^2 +8.50\ B^2 +2.75\ C^2$$

$$\mathbf{Permeation@24h} = +73.00 +2.12A +6.37B +0.7500C -0.5000AB -0.2500AC -0.2500BC +1.00A^2 +0.0000B^2 +1.25C^2$$

The coded factors equation can be used to predict the response for given levels of each factor. By default, the high levels of the factors are coded as +1, and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients (Fig 5).

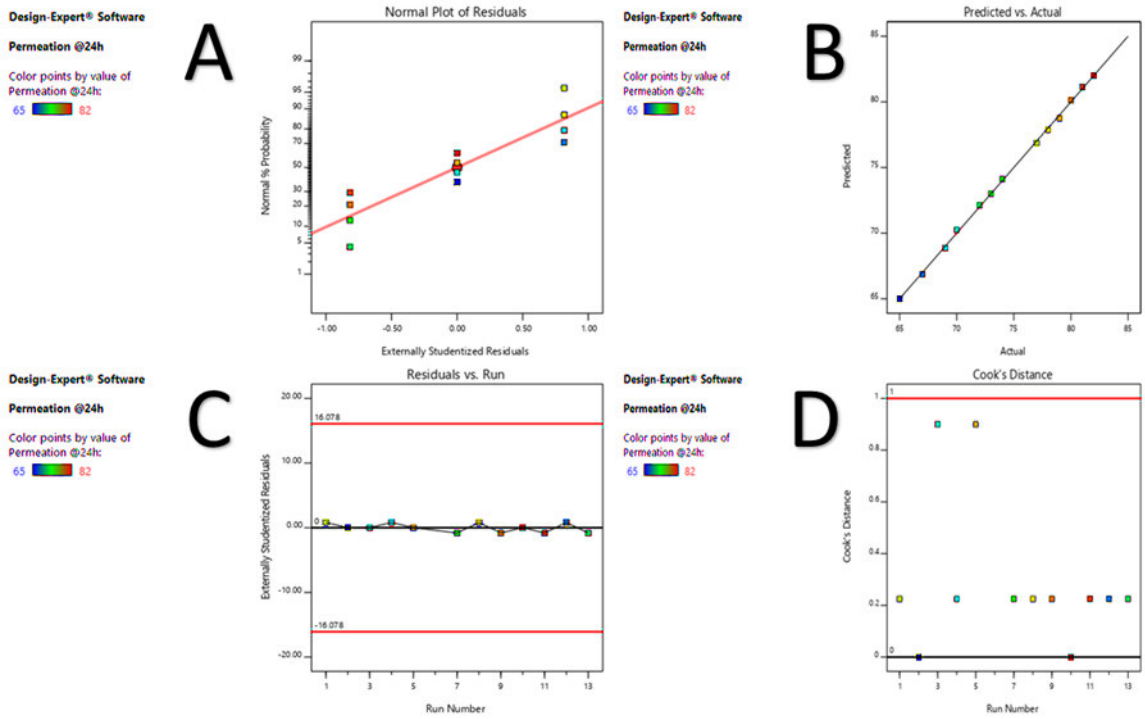
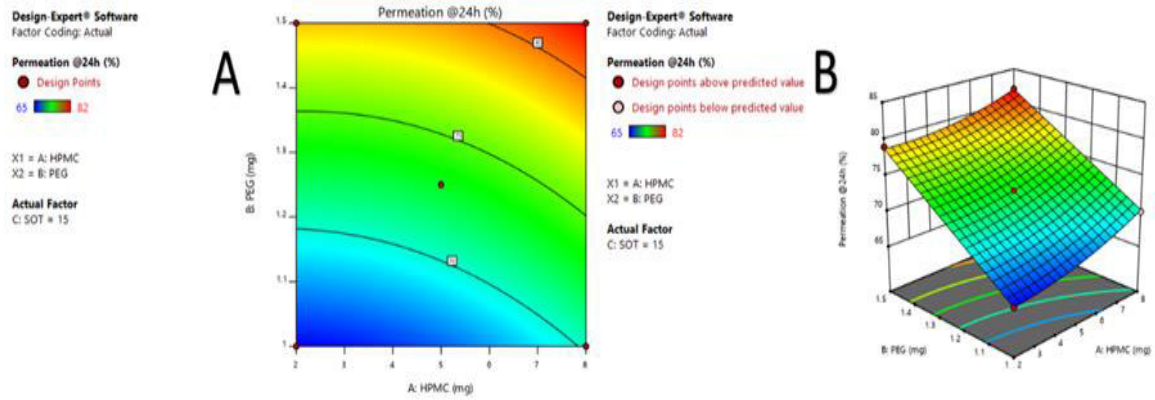


Fig 5: A) Normal plot of residual, B) Predicted vs Actual, C) Residual vs Run, D) Cook's distance



6. DISCUSSION

Transdermal drug delivery systems (TDDS) represent an innovative approach to drug administration that has gained significant attention in recent years. These systems offer several advantages over traditional routes such as oral or injectable delivery[16]. TDDS provides controlled and sustained release of drugs through the skin, allowing for improved patient compliance, reduced side effects, and enhanced bioavailability[17]. Transdermal delivery holds significant promise for drugs like chlorpheniramine maleate (CPM), a commonly used antihistamine for allergy treatment. The key advantage lies in circumventing the first-pass metabolism that occurs when CPM is taken orally, often reducing drug bioavailability. By opting for transdermal delivery, the drug can directly enter the bloodstream through the skin, bypassing the liver's initial metabolic processes[18]. This approach has the potential to significantly enhance the efficacy of CPM and subsequently improve therapeutic outcomes for patients suffering from allergies. Ultimately, transdermal delivery offers a promising avenue to optimize the pharmacological benefits of CPM, potentially leading to more effective and reliable allergy treatment [19]. The formulation of transdermal patches for the delivery of chlorpheniramine (CPM) is a multifaceted process that necessitates meticulous consideration of several critical variables, including the choice and concentration of polymers, selection of appropriate plasticizers, and the precise method of preparation[20]. Employing advanced methodologies like the Box-Behnken design (BBD) proves invaluable in this evaluation, as it enables a systematic and organized exploration of these variables [21]. Through BBD, various combinations of these key factors can be tested, controlled, and efficiently, facilitating the optimization of transdermal patch properties. This approach not only streamlines the development process but also enhances the likelihood of achieving the desired characteristics for effective CPM delivery, ultimately contributing to advancing transdermal drug delivery systems in the pharmaceutical field [22]. Indeed, Hydroxypropyl Methylcellulose (HPMC) and Polyethylene Glycol (PEG) are commonly employed as essential components in transdermal patch formulations. HPMC is a hydrophilic polymer frequently used in transdermal patches. It plays a crucial role in controlling the release of the drug from the patch. By adjusting the concentration of HPMC, you can modulate the rate at

which the drug is released, thereby achieving the desired therapeutic effect. HPMC forms a gel-like matrix when it comes into contact with skin moisture, helping to control drug diffusion and maintain a consistent release rate over time. PEG is commonly utilized as a plasticizer in transdermal patch formulations[23]. Plasticizers enhance the flexibility and elasticity of the patch, making it more comfortable for application and wear on the skin. PEG can also act as a solubilizing agent, aiding in the dispersion of the drug within the patch matrix. Additionally, it can improve the drug's solubility and enhance its permeation through the skin. Indeed, meticulous adjustment of the concentrations of Hydroxypropyl Methylcellulose (HPMC) and Polyethylene Glycol (PEG) in transdermal patch formulations is a critical strategy for tailoring the release kinetics and skin permeation properties of drugs, ultimately enabling precise control over drug delivery and absorption. These components are pivotal in optimizing transdermal drug delivery systems for chlorpheniramine (CPM) and a wide range of medications[24]. The ability to fine-tune the release rate of a drug and enhance its permeation through the skin is fundamental to achieving therapeutic precision and efficacy. Different drugs may have varying requirements for release profiles and skin permeability, making the customization of these parameters essential in designing effective transdermal delivery systems. The versatility offered by HPMC and PEG in patch formulations empowers researchers and pharmaceutical developers to address specific patient needs and optimize drug delivery for diverse therapeutic applications. Their careful selection and optimization are critical aspects of pharmaceutical research aimed at enhancing the effectiveness of transdermal drug delivery for many medications, including CPM[25]. A battery of rigorous tests is conducted to assess the performance of transdermal patches comprehensively. These tests provide critical information about the patch's effectiveness in delivering the drug and ensuring consistent dosing[26]. Firstly, drug release studies are crucial for understanding how the drug is released from the patch over time. They help determine the rate and extent of drug release, ensuring that it adheres to the desired release profile. By monitoring drug release, researchers can assess whether the patch provides the intended therapeutic effect[27]. Secondly, drug content uniformity is essential to guarantee accurate dosing. This test assesses the uniform distribution of the drug within the patch. Drug content variation can lead to inconsistent therapeutic outcomes, so maintaining uniformity is essential[28]. Thirdly, permeation studies investigate the ability of the drug to pass through the skin barrier and enter the bloodstream. These studies help determine the patch's efficiency in delivering the drug through the skin. The rate and extent of drug permeation are critical factors in evaluating the patch's efficacy[29]. Additionally, assessing whether the patch formulation causes skin irritation or sensitization reactions in users is essential. Skin compatibility studies help ensure that the patch is safe and well-tolerated when applied to the skin. Furthermore, assessing the patch's adhesive properties and wearability is important for user comfort and convenience. Adhesion studies evaluate how well the patch adheres to the skin, while wear studies consider the patch's flexibility and durability during extended wear. Moreover, stability testing is conducted under various storage conditions to ensure the transdermal patch maintains its integrity and drug potency over time. It helps determine the patch's shelf life and storage requirements. Finally, in some cases, bioavailability and pharmacokinetic studies may be conducted to assess how the drug is absorbed, distributed, metabolized, and eliminated from the body when delivered through the transdermal patch compared to other routes of administration. These tests provide a comprehensive evaluation of transdermal patches, ensuring their safety, efficacy, and reliability in delivering drugs like CPM through the skin. This rigorous testing process is essential in developing effective, patient-friendly transdermal drug delivery systems[30]. One crucial aspect of transdermal drug delivery is bioavailability, which refers to the fraction of the drug that reaches the systemic circulation. Comparative studies between transdermal patches and orally administered formulations provide valuable insights into the bioavailability of CPM. These studies often reveal that transdermal patches offer a controlled and sustained delivery mechanism, resulting in a more predictable pharmacokinetic profile and reduced side effects compared to oral administration. Recent advancements in transdermal drug delivery systems include the development of innovative delivery technologies, such as microneedle patches and iontophoresis, which further enhance the efficiency and convenience of transdermal drug administration. Transdermal drug delivery systems have the potential to revolutionize the delivery of drugs like CPM. These systems can offer controlled drug release, improved bioavailability, and enhanced patient compliance through systematic formulation optimization and comprehensive evaluation.

7. CONCLUSION

Our study has successfully developed transdermal patches containing chlorpheniramine maleate (CPM) to provide controlled and sustained drug release through the skin. Transdermal drug delivery systems (TDDS) are promising, offering several advantages, including enhanced patient compliance, minimized side effects, and improved drug bioavailability. The key components of our transdermal patch formulation, HPMC (a polymer) and PEG (a plasticizer), played critical roles in achieving these objectives. HPMC formed a gel-like matrix upon contact with skin moisture, effectively controlling drug diffusion and ensuring a consistent release rate. Meanwhile, PEG, commonly used as a plasticizer, contributed to the flexibility and elasticity of the patches, enhancing their overall performance. One of the paramount considerations in transdermal drug delivery is bioavailability, which refers to the fraction of the drug that enters systemic circulation. In this context, our study conducted comparative analyses between transdermal patches and orally administered formulations. These comparisons provided valuable insights into the bioavailability of CPM through different routes of administration. The findings of our research not only demonstrate the successful development of CPM transdermal patches but underscore the significance of these patches in optimizing drug delivery. Through their ability to maintain a consistent release rate and improve bioavailability, transdermal patches represent a promising avenue for administering medications, including anti-allergic agents like CPM. This study contributes to the growing body of knowledge in pharmaceutical science and emphasizes the potential benefits of transdermal drug delivery systems in clinical practice.

8. AUTHORS CONTRIBUTION STATEMENT

Hindustan Abdul Ahad conceived the notion of creating a transdermal patch for CPM. Subsequently, a collaborative effort between Dheeraj and Hindustan Abdul Ahad ensued, involving an in-depth exploration of existing literature and the

formulation process. Haranath utilized OBD software to establish a robust formulation. Following this, Dheeraj meticulously executed a series of comprehensive evaluation tests.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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