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A QbD Approach In Designing and Evaluation of Piroxicam Transdermal Patches by Using Design Expert Software

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ABSTRACT

Transdermal patches have a high systemic impact and may increase absorption by bypassing hepatic first-pass metabolism. A transdermal therapeutic system allows drugs to be continuously administered into the systemic bloodstream at a predetermined rate through unbroken skin over an extended period of time. When piroxicam (PXM) is taken orally, it can cause headaches, exhaustion, dry mouth, nose, and throat, nausea, vomiting, and sleepiness. It is also insoluble in water, so its allure is tainted by its decomposition. These issues are avoided by using a solvent-casting technique on a mercury surface in PXM matrix-type transdermal patches. In HPMC E50LV and Eudragit RS 100 transdermal patches, glycerine (plasticizer) is produced through solvent evaporation and a film-forming polymer. The FTIR method will be used aesthetics, breadth, weight difference, folding durability, moisture content, tensile strength, and percentage of PXM content were all deemed satisfactory on a physical level. According to the study, PXM release from transdermal patches can be improved by combining HPMC E50LV (400 mg) and Eudragit RS 100 (300 mg) with glycerine as a plasticize

Keywords: Piroxicam, Transdermal patches, QbD Approach

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INTRODUCTION

This century has seen a number of incredible advances in pharmaceutical sciences, particularly in the area of drug delivery methods. As people become more aware that conventionally used medications can be overly harmful and sometimes useless, more emphasis is being placed on innovative drug delivery technologies. As a result, in addition to therapeutic efficacy, the cost of developing newer drug delivery systems is a driving force behind their development. Traditional drug formulations, such as tablets, capsules, injections, and oral liquids given in multiple doses, produce large fluctuations in drug concentration in the bloodstream [1,2,3].

Development in Transdermal Drug Delivery

The skin was thought to be a solid barrier. During World War II, munitions workers experienced fewer angina attacks while working with nitroglycerin at the turn of the century. This has called into question the long-held belief that the skin is a perfect protective barrier, as well as sparked intense research into the feasibility of transdermal drug delivery for systemic medication [4,5,6,7,8].

Several transdermal drug delivery systems (TDDS) have recently been developed to achieve the goal of systemic medication via transdermal controlled pharmaceutical delivery. In addition to currently marketed formulations, new drugs are being developed using transdermal systems due to the inherent benefits of administration via this route**.**

Skin structure and barrier properties

The skin is the most accessible organ in the body. Its primary functions are protection, temperature regulation, and water output and sensation control. It receives approximately one-third of the blood that circulates throughout the body [9,10]. The skin is divided into two layers: the dermis, 777It may also carry the major blood vessels and nerves to the skin and contain sensory pressure organs [11].

Technologies of transdermal drug delivery systems

To provide a mechanism for rate control over the release and transdermal permeation of drugs, a number of methods have been developed with success. To be more specific, the design of the TDDS is based on two concepts: a skin-controlled device (of the monolith type) and a system-controlled device (of the reservoir type). These two ideas serve as the foundation for the others, [12].

Device controlled by the skin:

Monolith or Matrix System) It is intended to control the rate at which the drug diffuses into the body by relying on the skin

System-Controlled Device :(Reservoir (Or) Membrane system)

The transdermal system provides the majority of control over the rate of medication entry into the

body. Other functional elements of system-controlled devices include a rate-controlling membrane, a reservoir containing the drug (often in liquid or generic form), a sticky layer, and protective layers. This type of system is advantageous when the required rate of drug delivery is much slower than that through the skin [13].

1. Polymer membrane permeation - controlled systems:
2. Matrix diffusion-controlled systems:
3. Adhesive diffusion-controlled systems:
4. .4. Micro reservoir /micro-sealed controlled systems:

Advantages of TDDS

The merits are as follows

- Prevents gastrointestinal absorption fluctuations due to to pH, enzyme activity, and drug-food interactions.
- It replaces oral administration
- In the event of adverse reactions, it can be stopped easily by peeling off the patch [14,15,16,17].

Limitations of TDDS

The limitations are as listed

- TDDS cannot be used for the drugs.
- The limited time that the patch can remain affixed.
- Variable intra-and inter-individual percutaneous absorption efficient [18,19,20,21].

Objectives

To deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intra patient variation. To design a quality product and its manufacturing process to consistently deliver the intend of the product. Performed FTIR studies to know the compatibility of drug and excipients. Determination of physicochemical properties.

QBD (Quality by design)

Quality by Design (QBD), is an essential part of the modern approach to pharmaceutical quality, The concept of QBD was mentioned in the ICH Q8 guideline, which states that “quality cannot be tested into products, i.e., quality should be built in by design” According to ICH Q8 QBD is defined as A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

QBD contain these five steps are:

I. Define: The intended improvement should be clearly stated

II. Measure: The critical product performance attributes should be measured to see if they are out of specification and used to the sigma level of the process.

III. Analyze: When the sigma level is below the target, steps should be taken to increase it, starting by identifying the most significant causes of the excessive variability.

IV. Improve: The process should be redesigned and/ or process controls should be incorporated to eliminate or attenuate the significant root causes of variance.

V. Control: The improved manufacturing process should be evaluated and maintained.

Piroxicam:

Piroxicam is a non steroidal anti-inflammatory drug (NSAID) of the oxicam class used to relieve the symptoms of painful inflammatory conditions like arthritis.[22,23] Piroxicam works by preventing the production of endogenous prostaglandins which are involved in the mediation of pain, stiffness, tenderness and swelling.[3] It is used in the treatment of certain inflammatory conditions like rheumatoid and osteoarthritis, primary dysmenorrhoea, postoperative pain; and act as an analgesic, especially where there is an inflammatory component.[22]

Mechanism of action:

The anti-inflammatory effect of piroxicam may result from the reversible inhibition of cyclooxygenase, causing the peripheral inhibition of prostaglandin synthesis. The prostaglandins are produced by the enzyme called Cox-1. Piroxicam blocks the Cox-1 enzyme, resulting into the disruption of production of prostaglandins. Piroxicam also inhibits the migration of leukocytes into sites of inflammation and prevents the formation of thromboxane A2, an aggregating agent, by the platelets.

Formulation of Transdermal Patches

In the present study, matrix-type transdermal patches (TDPs) of PXM were prepared by moulding techniques. A flat circular glass mould having a diameter of 4.5 cm and height of 1 cm with a total surface area of 15.91 cm^2 was fabricated for this purpose [24,25,26].

Preparation of casting solutions:

The casting solutions were prepared by dissolving weighed quantities of polymers in a solvent mixture of chloroform and methanol at a 1:1 ratio. The drug, plasticizer and permeation enhancers were then added to the various polymer solutions individually and thoroughly mixed from a homogenous mixture. It was placed aside without any disturbances to allow the entrapped air to bubble out.

Preparation of TDPs

Approximately 3 ml of casting solutions were pipetted into elliptical glass moulds with specific

casting surfaces to contain the contents. In order to remove any remaining solvents, the TDPs were dried at 40–45 °C for 30 min after the glass moulds with casting solutions were let to dry at RT for 24 h. The TDPs were taken off and sliced into 4.4 cm-diameter discs (15.21 cm^2 surface area). For additional research, these TDPs were packaged in aluminium foil and kept in a desiccator (table 1.).

Table 1: Compositions of TDPs of PXM

Formulation	PXM (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

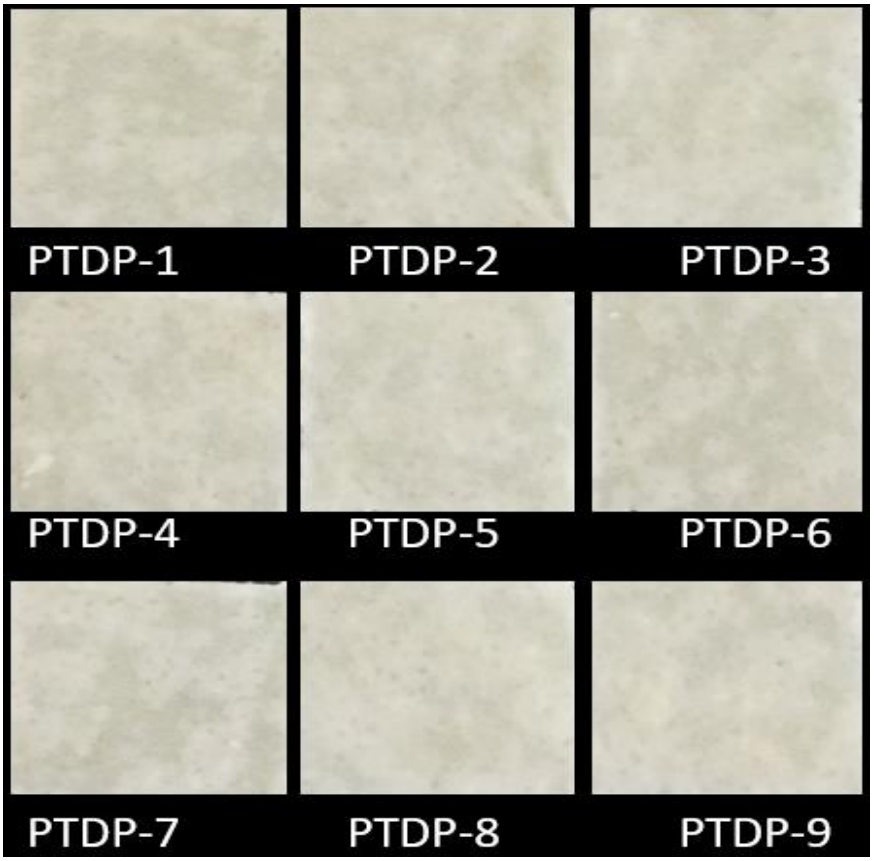

Figure 1: Various transdermal TDPs of PXM

EVALUATIONS

The following evaluation tests were performed [27, 28, 29].

Compatibility studies

The FTIR spectrum of the PXM with polymers was analyzed based on the infrared spectrum measured. PXM was mixed and triturated with dry KBr, pellets were made, and the spectrums were obtained.

Physical appearance

All PTDPs were visually reviewed for colour, clarity, flexibility, and smoothness. The thickness of PTDP was measured at three locations with a micrometre and a mean value was calculated.

Uniformity of weight

Three PTDP were randomly selected for each formulation. The mean weight of 6 PTDP from each batch was calculated after weighing PTDP from each batch separately.

Folding Endurance (FE)

In this experiment, a PTDP was folded until it broke recurrently in the same spot. A film's FE is quantified by the number of times it can be pleated in the same place deprived of breaks.

Tensile strength

A 40 x 15 mm PTDP was attached to adhesive tape at one end to give the PTDP support when it was placed inside the patch holder (figure 2). The other end of the PTDP was kept straight while widening by inserting a small pin among the adhesive tape. The glue tape was punctured near the pin where the hook was implanted. The authors affixed a small pin to the other end of the thread, pass it over the pulley, and tie a thread to this hook to hold the weights. A small pointer moves over the graph paper on the base plate as it moves along the thread. The tensile strength of the PTDP was controlled by a pulley system. Weights were gradually added to the pan to elevate its pulling force. A PTDP's breaking force was calculated by measuring how much weight it takes to break it.

Figure 2: Tensile strength apparatus

Moisture content

In desiccators with $CaCl_2$, the PTDP is kept at RT for 24 h. At every specified interval, the PTDPs are weighed again until their weight is constant. Here is the formula to calculate the moisture content.

$$\text{Moisture content } \frac{\text{Initial weight} - \text{Final weight}}{9\text{Final weight}} X100$$

Assay

1 cm^2 of each PTDP was cut, and 100 ml of phosphate-buffered saline was included. A magnetic bead was used to stir the medium. By using Whatman filter paper, the contents of the tube were filtered and spectrophotometrically analyzed for drug content at 336 nm against a blank. I repeated the procedure to get a constant result.

In Vitro Diffusion Study

In vitro diffusion studies were led using FD cell receptor sections with a capacity of 22 ml. 22 mL of phosphate buffer, pH 7.4, was decanted into the receiver section. To mount the cellophane membrane on the donor compartment, the PTDP was firmly pressed onto the centre of the cellophane membrane. Once this was done, the donor compartment was located so that the membrane surface just touched the surface of the receptor fluid. A water bath was used to keep the entire assembly at 32°C. Samples were taken at different intervals and analyzed for drug content every 12 h. During each time interval, equal volumes of buffer solution were included in the receptor cell (figure 3)

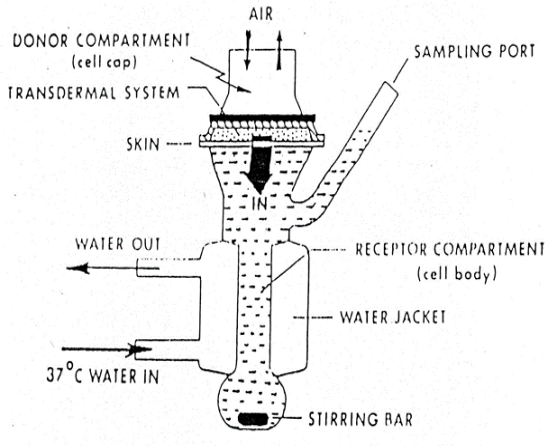

Figure 3: Franz Diffusion Cell

RESULTS AND DISCUSSION

FTIR Data

The FTIR techniques were used here to study the chemical and physical interactions between the PXM, and the excipients used (Figure 4). It was observed that the main peaks in the IR spectra of a

mixture of PXM and polymers did not change, indicating no physical interaction between the PXM and HPMC E50LV and Eudragit RS 100.

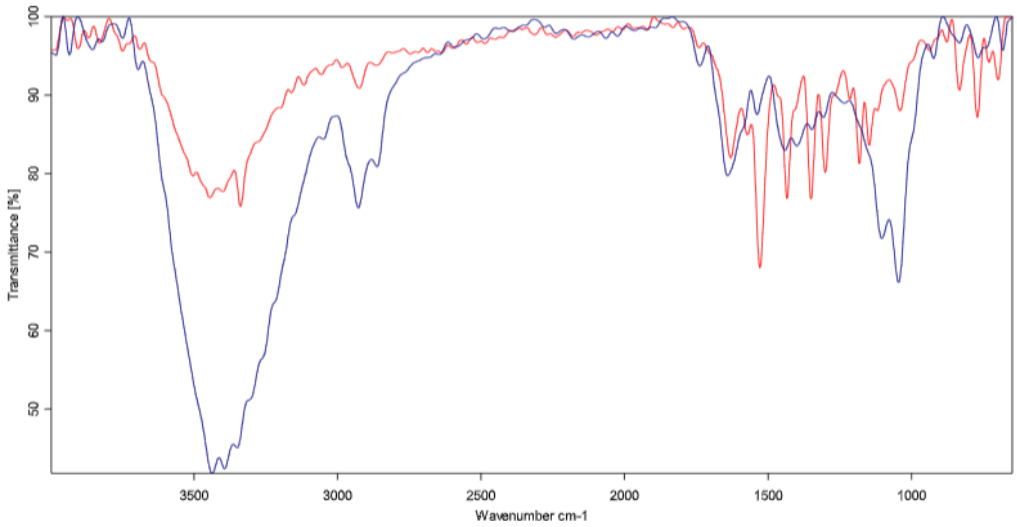

Figure 4: FTIR spectra of PXM and with its excipients

Physical and Chemical Properties of the PTDP

The physical and chemical properties of the PTDP, including look, thickness, weight uniformity, FE, moisture content, tensile strength, per cent elongation at break, and per cent drug content, were satisfactory (Table 2; Figure 5). The physical appearance was found to be good. The thickness was found to be uniform and ranged from 44.17±0.95 to 47.14±2.00µm. The weight of the patches was ranged from 250.51±9.5 to 280.11±5.2 mg and found to be uniform. The folding endurance was good in the PTDP-5 at 165±6 times, whereas other patches ranged from 124±5 to 165±6 times. The moisture content was minimal in the patches and ranged from 4.1±0.09 to 4.6±0.06%. PXM content was uniform and ranged from 94.58±6.25 to 98.65±4.51 %. The maximum DP@24h is shown by PTDP-1 and PTDP-5 PTDP. The PTDP also appears to fold best with the PTDP-8 and PTDP-9.

Table 2: Physicochemical of PTDP

Formulation	Physical appearance	Thickness (µm)	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

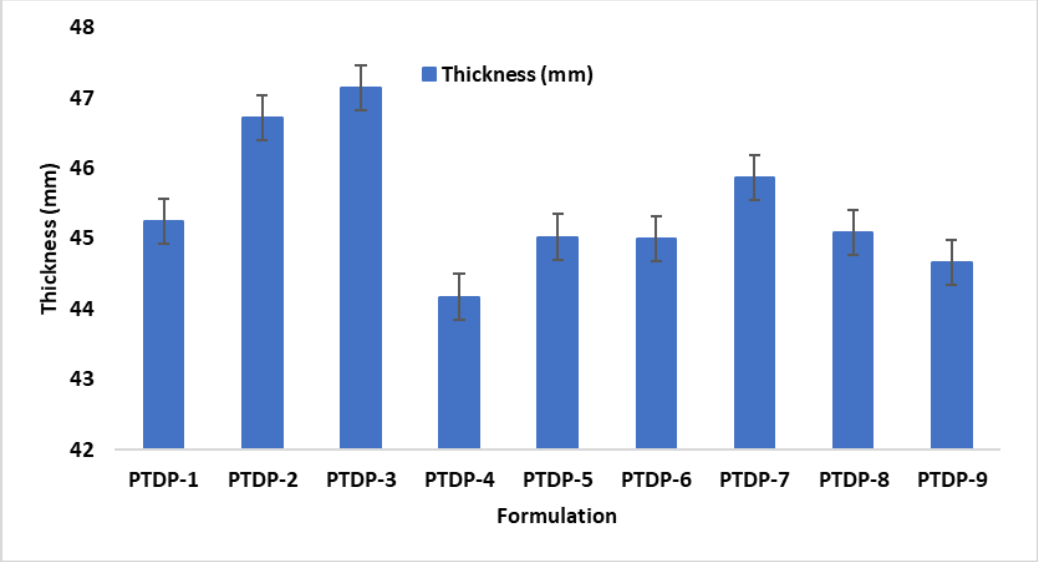

Figure 5: Thickness of the PTDP

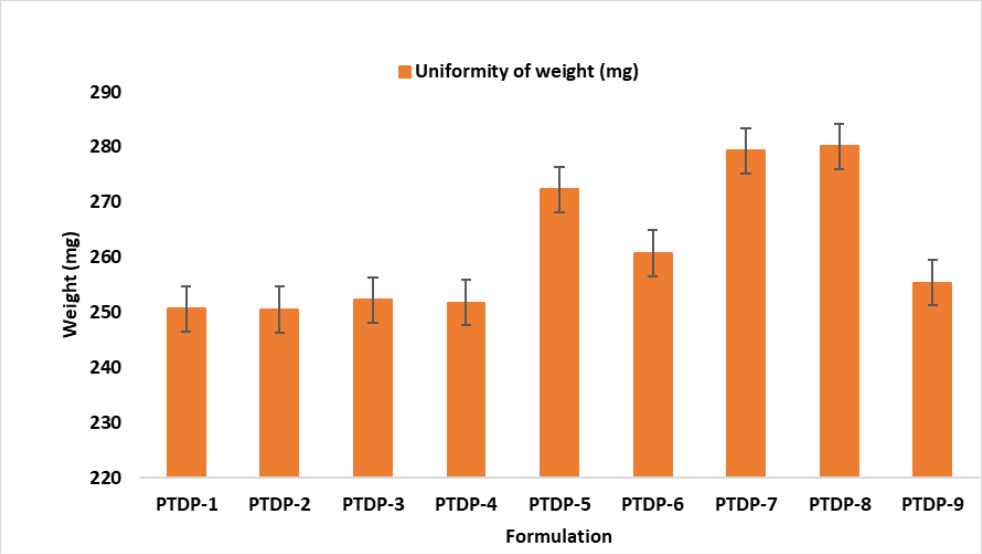

Figure 6: Uniformity of the weights of the PTDP

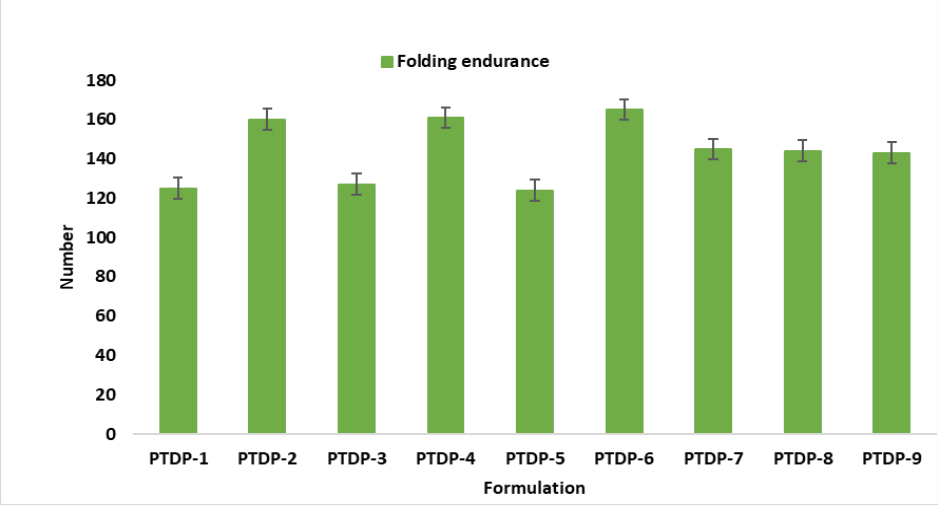

Figure 7: Folding endurance of the PTDP

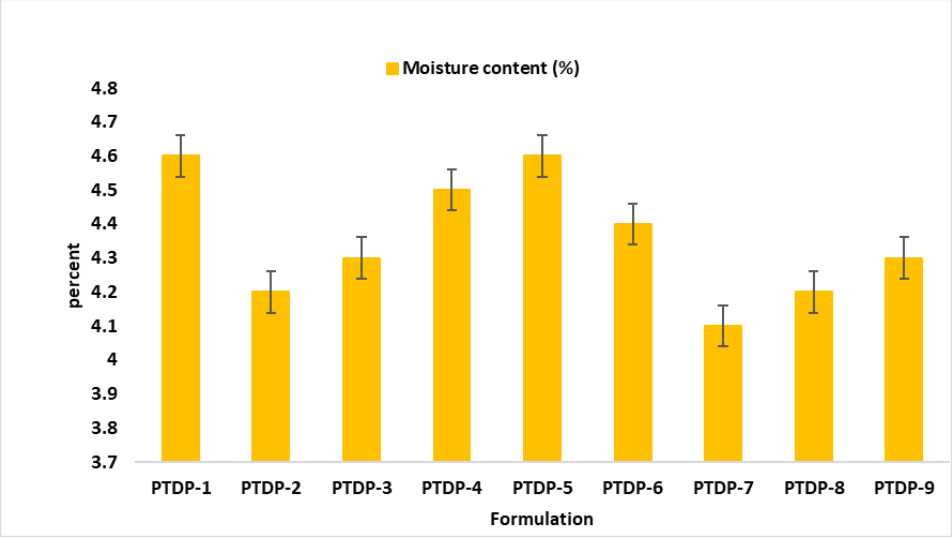

Figure 8: Moisture content of the PTDP

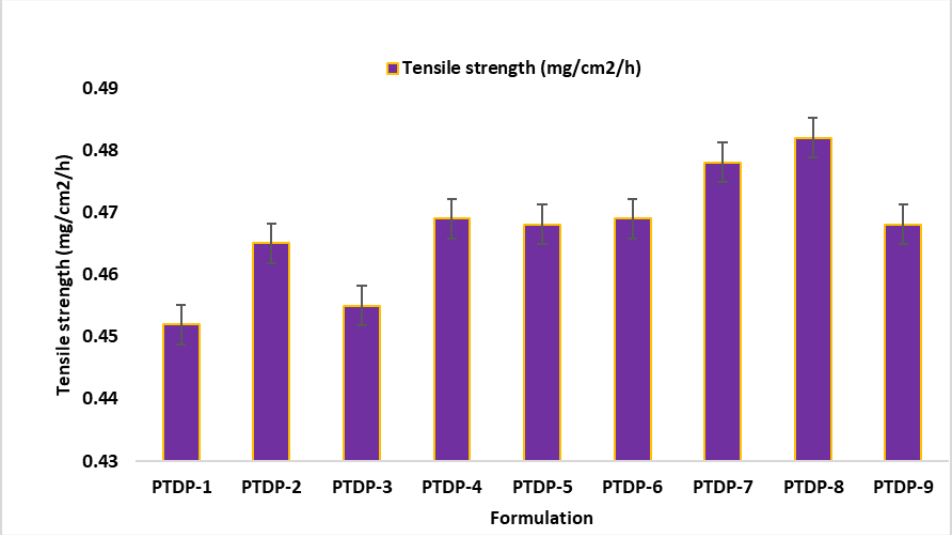

Figure 9: Tensile strengths of the PTDP

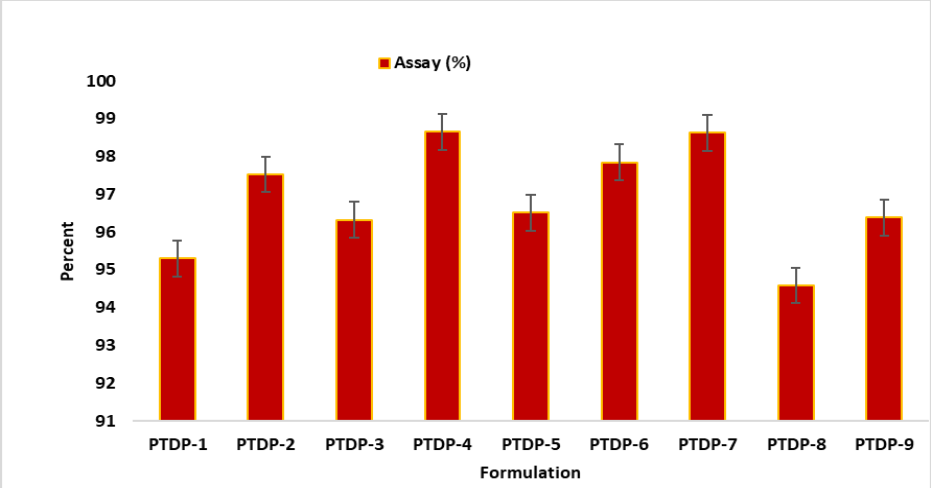

Figure 10: Assay of the PTDP

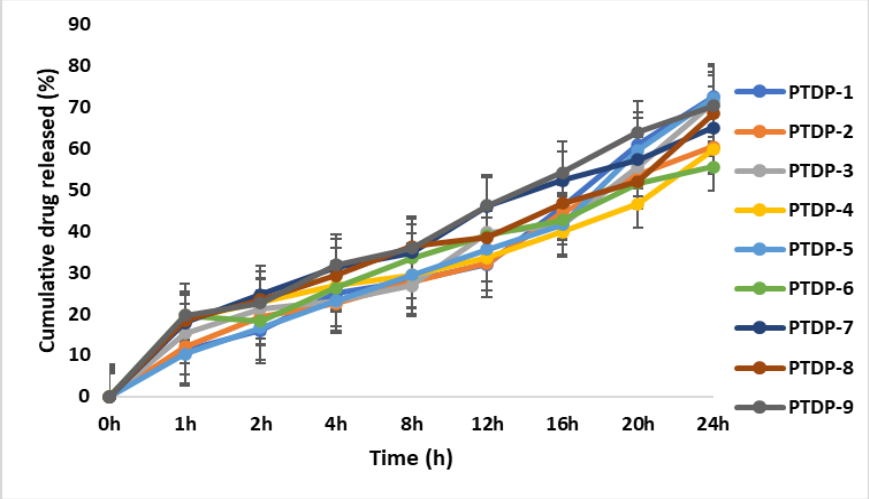

Figure 11: In vitro PXM permeation graph till 24 h

DESIGN EXPORT SOFTWARE ANALYSIS

The responses, namely FE and DP@24h when placed in Design-Expert software and analyzed the fit summary (Table 3) and ANOVA details (Table 4) were produced.

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		
Core Total	310.59	8			

The model's F-value of 58.37 implies that the model is significant. It was only a 0.35% chance that an F-value this large could befall due to noise.

Significant model footings have P-values <0.05. Here, A is a significant model term. A P-value over 0.1000 indicates that the model rapports are not significant. The model's F-value of 27.35 indicates that it is significant. Due to noise-values of <0.05, it was only a 1.05% chance of an F-value this large occurring. These are significant terms in the model. A value >0.1000 indicates that the model relations are not significant. Model reduction may be beneficial if your model contains many insignificant terms (excluding those necessary to support the hierarchy). In terms of FE, the final equation had the following coded factors.

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

By expressing the equation in terms of coded factors, predictions about the response to a given level of each factor can be made. High factor levels are coded as +1 and those that are low are coded as -1 by default. Comparing the coefficients of the factors using the coded equation is useful for identifying the relative impact of the factors. DP is calculated as:

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

Using the equation based on coded factors, it is possible to make predictions about the response given a particular level of each factor. A factor with a high level (+1), while one with a low level (-1). The factor coefficients can be compared in the coded equation to determine the relative impact of each factor.

Following the graphs in figure 12 and 17, the FE response and DP@24h response result points were linear. There was a close correlation between the residual vs. predicted values (Figure 13 and 18). Figure 14 and 19 show that the cook's distance was below the red line for FE and DP@24h. Figure 15 and 20, as well as figure 16 and 21, display contour and 3D response surface plots illustrating the relationship between the factors and the responses. The results indicate how HPMC E50LV and Eudragit RS 100 affect FE and DR at 24 h.

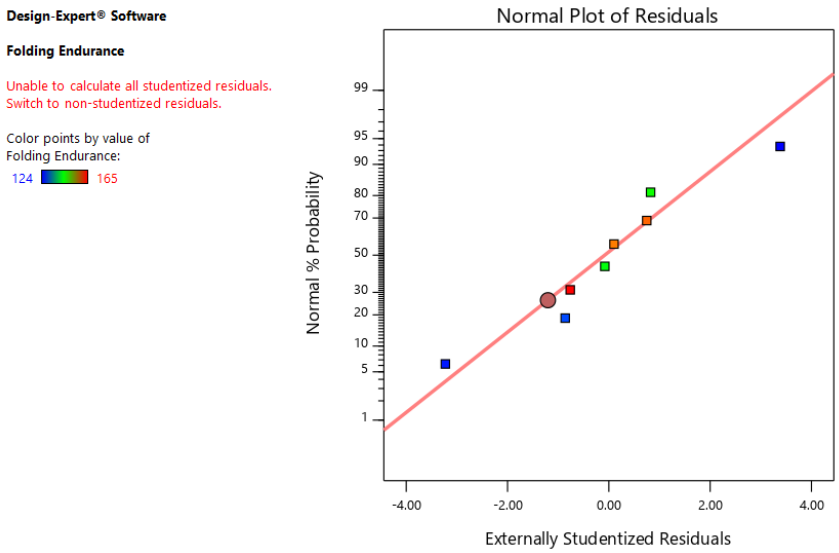

Figure 12: Normal plot showing the effect of HPMC E50LV and Eudragit RS 100 on folding endurance

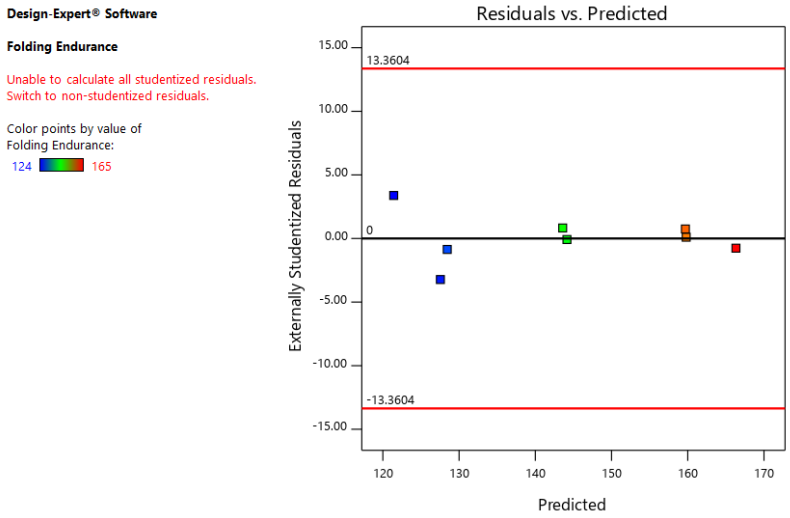

Figure 13: Residual vs. predicted plot showing the effect of HPMC E50LV and Eudragit RS 100 on folding endurance

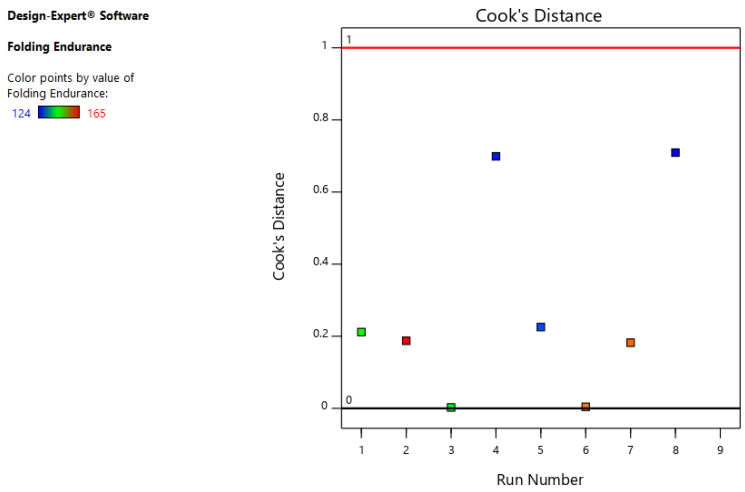

Figure 14: Cook's distance plot showing the effect of HPMC E50LV and Eudragit RS 100 on folding endurance

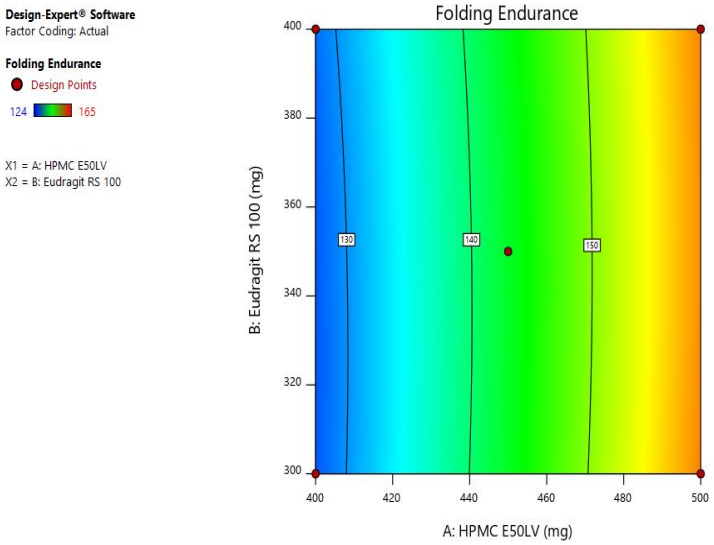

Figure 15: Contour plot showing the effect of HPMC E50LV and Eudragit RS 100 on folding endurance

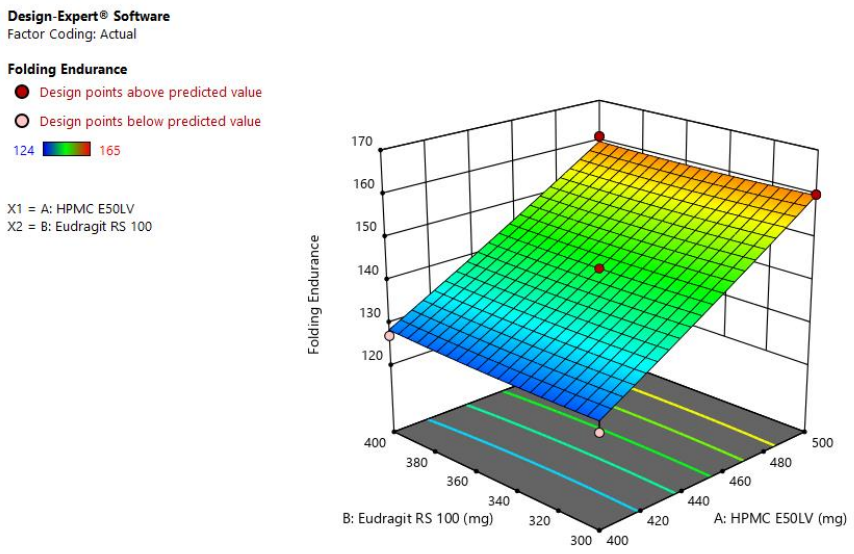

Figure 16: 3D plot showing the effect of HPMC E50LV and Eudragit RS 100 on folding endurance

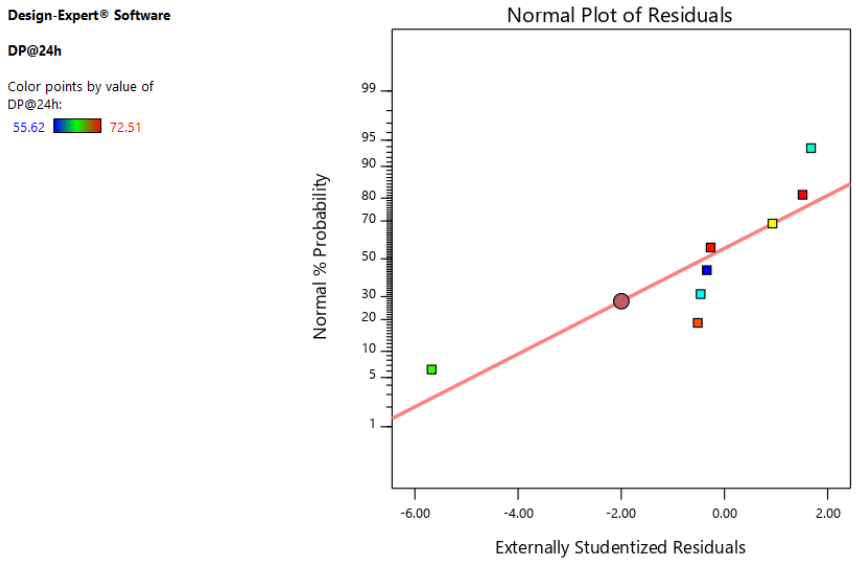

Figure 17: Normal plot showing the effect of HPMC E50LV and Eudragit RS 100 on DP@24h

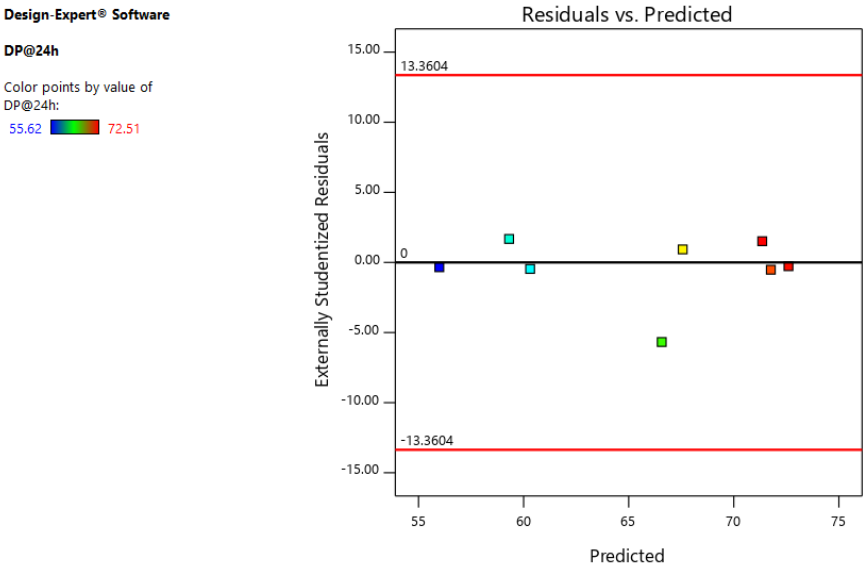

Figure 18: Residual. vs. predicted plot showing the effect of HPMC E50LV and Eudragit RS 100 on DR @ 24h

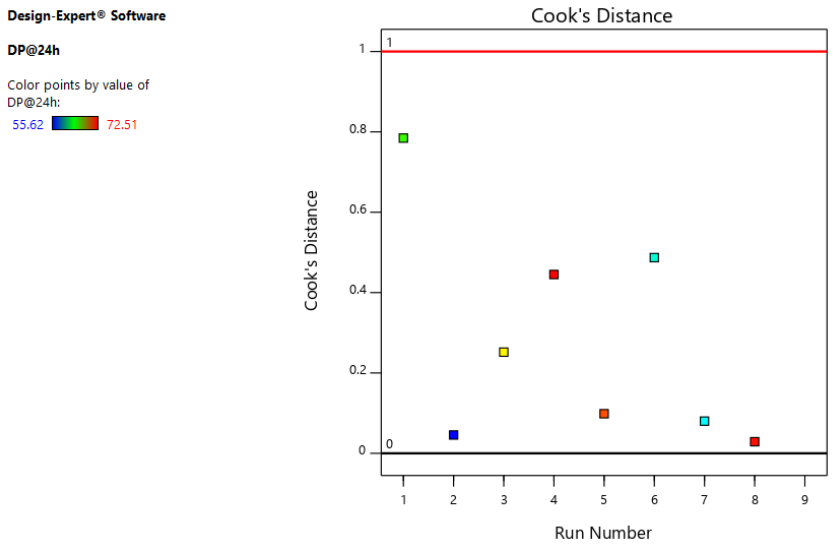

Figure 19: Cook's distance plot showing the effect of HPMC E50LV and Eudragit RS 100 on DP@24h

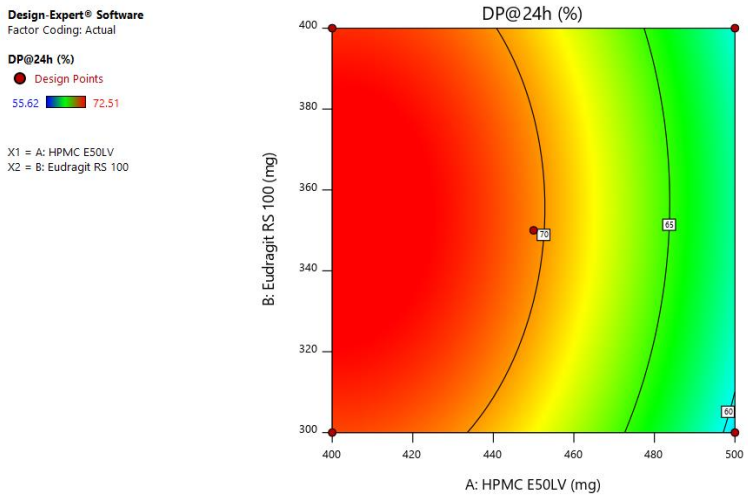

Figure 20: Contour plot showing the effect of HPMC E50LV and Eudragit RS 100 on DP@24h

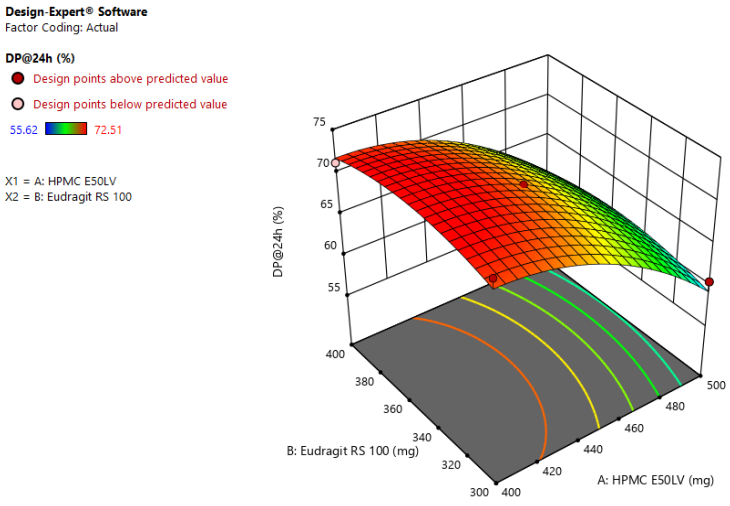

Figure 21: 3D plot showing the effect of HPMC E50LV and Eudragit RS 100 on DP@24hr

CONCLUSION

Several PXM-TDPs were produced by dissolving HPMC E50LV and Eudragit RS 100 in dichloromethane solvent and adding glycerin as a permeability enhancer. The FTIR spectra of a mixture of PXM and polymers did not affect the excipients used as the primary peaks of PXM, demonstrating that there were no chemical or physical interactions between the PXM. This shows that there is no physical interaction between the PXM, HPMC E50LV, and Eudragit RS 100. The PTDP's physical and chemical properties, including thickness, weight uniformity, FE, moisture content, tensile strength, percent elongation at break, and percent drug content, were all excellent. The outward appearance was judged acceptable. It was found that the thickness was constant. Folding endurance in the PTDP-5 was good. Very little moisture is present in the TDPs. All TDPs had PXM content that was the same. The maximum DP@24h is shown on PTDP-1. PTDP-induced

PXM penetration lasted for more than 24 hours, per in-vitro drug permeation. After inserting and analyzing the responses, FE and DR@24h, in Design-Expert software, the fit summary and ANOVA details were created. The residual and anticipated values had a close relationship. The locations in the cook's distance for FE and DR@24h were below the red line. The relationship between the factors and the responses is displayed by the 3D response surface and contour plots.

According to the study, PXM-TDPs were created using HPMC E50 and Eudragit RS 100 (mg), and the impact of these elements on the responses (folding endurance and drug permeation) was investigated. Utilizing the programme Design Export.

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