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Original Article

OPTIMIZING TRANSDERMAL PATCH FORMULATION FOR ENHANCED DELIVERY OF RIVAROXABAN: A COMPREHENSIVE DESIGN OF EXPERIMENTS APPROACH

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ABSTRACT

Objective: To optimize Trans Dermal Patches (TDPs) of rivaroxaban using Poly Vinyl Pyrrolidone (PVP K30) and Hydroxypropyl Methyl Cellulose E50(HPMC E50) as hydrophilic polymers, Propylene Glycol(PG) as a plasticizer, and permeation enhancer.

Methods: TDPs were crafted using a solvent casting technique with a 2-level, 3-factor factorial design. These patches were assessed for thickness, folding endurance, *in vitro* drug release, drug content, and moisture uptake and loss. An 8-stage diffusion cell apparatus facilitated *in vitro* drug release testing. The independent variables were HPMC E50, PVP K30, and PG. The change in the concentration of these independent variables resulted in the optimization of the transdermal patch. The dependent variables were the thickness, folding endurance, and *in vitro* diffusion.

Results: The patch thickness ranged from 0.311±0.3 to 0.334±0.6. Folding endurance ranged from 58±0.7 92±6. The *in vitro* drug release ranged from 52.36% to 95.58%. The percentage drug content ranged from 83.58±0.4 to 95.26±0.5. The percentage of moisture content absorbed ranged from 21.36±0.13% to 25.54±0.26%. The percentage of moisture lost ranged from 1.01% to 2.31%.

Conclusion: PG increased the release of rivaroxaban because it permeated the membrane. HPMC E50 is highly soluble. Thus, rivaroxaban patches are potentially suitable transdermal drug delivery systems.

Keywords: Rivaroxaban, Transdermal patches, Factorial design, *In vitro* drug release, Hydroxypropyl methylcellulose

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INTRODUCTION

TDDS (Transdermal Drug Delivery Systems) represents a significant advancement in medication administration, utilizing patches or semi-solid formulations applied topically to achieve systemic effects at a controlled rate. In contrast to traditional administration routes, they offer distinct advantages, such as precise medication release, bypassing hepatic metabolism, and prolonged duration of action [1, 2]. Rivaroxaban (RXB), a direct anticoagulant categorized as a factor Xa inhibitor, has garnered worldwide recognition for its effectiveness in managing a range of thromboembolic conditions such as atrial fibrillation, deep vein thrombosis, and pulmonary embolism [3, 4]. While RXB offers advantages over conventional anticoagulants, such as consistent pharmacokinetics and fewer drug interactions, its formulation encounters challenges due to its limited solubility and uneven bioavailability.

This study comprehensively addresses these formulation hurdles by focusing on designing pharmaceutical dosage forms tailored for RXB. Key considerations include enhancing drug solubility, ensuring stability, optimizing bioavailability, and assessing the feasibility of the formulation. By adopting a systematic approach, researchers and pharmaceutical scientists can effectively navigate these challenges, facilitating the development of dosage forms that promise optimal drug distribution, therapeutic efficacy, and patient adherence [5]. The novelty of this study lies in the development of a transdermal delivery system for RXB, a drug poised for significant market growth by 2030. This formulation capitalizes on the benefits TDPs (Trans Dermal Patches), effectively bypassing first-pass metabolism, a common drawback of oral delivery. Utilizing a 23-factorial design facilitated by Design Expert 11 software represents an innovative approach, allowing for precise formulation control that optimizes drug release, stability, and patient compliance. This investigation specifically targets the needs of bedridden patients and individuals with table *et al.* lergies, ensuring that the final product adheres to quality standards while enhancing patient adherence. A comprehensive evaluation of the key factors guarantees that the formulation meets these objectives.

The choice to prioritize TDPs arises from their appropriateness for administering to bedridden patients and those who are allergic to tablets. These formulations provide direct access to the systemic circulation, bypassing first-pass metabolism in the liver. PG (Propylene Glycol) was selected as a permeation enhancer because of its compatibility with the log P value of RXB (approximately 1.5) to enhance permeation.

MATERIALS AND METHODS

Materials

Rivaroxaban (Alphamed Formulations, Hyderabad), HPMC E50 (Hydroxypropyl Methyl Cellulose E50) (Thermo Fisher Scientific India Pvt. Ltd, Mumbai), PVP K30 (Poly Vinyl Pyrrolidone) (LOBA ChemiePvt. Ltd, Mumbai), Ethanol (Changshu Honsheng Fine Chemical Co., Ltd, China), PG (Propylene Glycol)(LOBA ChemiePvt. Ltd, Mumbai), Franz diffusion cell apparatus (Orchid Scientifics™), Film former (VJ Instruments, Maharashtra), UV-Visible spectrophotometer (Lab India Double Beam UV 3092, Mumbai), Differential Scanning Calorimetry (DSC) (TA instruments, Bangalore), Fourier transform infrared spectroscopy (FTIR) (Alpha Bruker, Chennai).

Methods

The process involved assessing various concentrations of PVP K30 (0.3 gm, 0.5 g) and HPMC E50 (1.5 gm, 2.5 g). HPMC E50 was dissolved in distilled water in a beaker using a magnetic stirrer to ensure gradual addition and prevent lump formation. Simultaneously, PVP K30 was mixed with ethanol in another beaker, and the required quantity of drug was added. The two solutions were stirred together for five minutes. Subsequently, PG was introduced into the mixture, which was stirred for an additional hour and left undisturbed for one day. TDPs were prepared by solvent casting under thorough stirring. After one day, the solution should achieve transparency. After attaining the required temperature, the backing membrane was attached to the film-

former. The solution was then spread onto the backing membrane and dried. It was covered with the release liner and the patch was cut into the desired shape.

Experimental design

The TDPs were fabricated using solvent casting. To optimize the formulation, a 2^3 factorial design was employed, encompassing two levels and three factors, HPMC E50, PVP K30, and PG, treated as independent variables. Thickness, folding endurance, and *in vitro* diffusion were dependent variables. The concentration levels for the factors were set at 1.5 and 2.5 for HPMC E50, 0.3 and 0.5 for PVP K30, and 2 and 4 for PG. Eight distinct combinations were prepared and subjected to comprehensive evaluation.

Fig. 1: Transdermal film

Table 1: Composition of 8 different TDPs formulations of RXB

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Drug	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
HPMC E50	1.5 gm	2.5 gm	1.5 gm	2.5 gm	1.5 gm	2.5 gm	1.5 gm	2.5 gm
PVPK30	0.3 gm	0.3 gm	0.5 gm	0.5 gm	0.3 gm	0.3 gm	0.5 gm	0.5 gm
PG	2 ml	2 ml	2 ml	2 ml	4 ml	4 ml	4 ml	4 ml
Ethanol	12 ml	12 ml	12 ml	12 ml	12 ml	12 ml	12 ml	12 ml
Distilled water	QS	QS	QS	QS	QS	QS	QS	QS

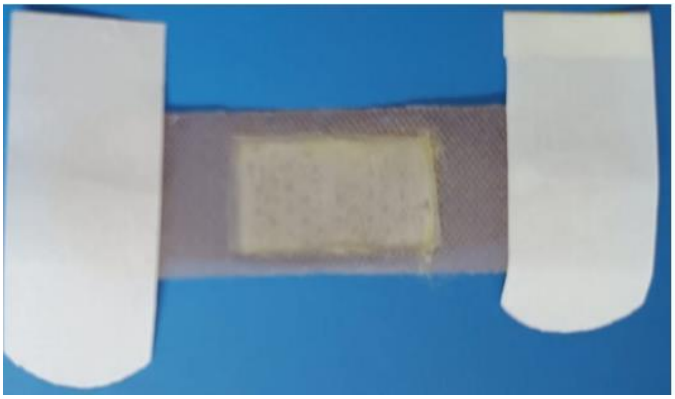

Fig. 2: Optimized RXB transdermal patch

Evaluation tests

Thickness

A precision thickness gauge, capable of detecting measurements as low as 1µm was used to assess the thickness of the films. This gauge, featuring pressure sensitivity and self-adjusting capabilities, effectively prevented the films from distorting when positioned between their jaws. Each film was carefully inserted between the teeth of the instrument, and five consistent measurements were taken, documenting both the instrument settings and readings obtained [6].

Folding endurance

Following folding in half, the film patch was gently opened using the fingers and thumb; this procedure is called "one folding." This procedure was repeated until the film fractured or displayed cracks. The folding endurance value was calculated by counting the total number of folds sustained by the film during this process [7].

***In vitro* skin permeation assay**

An *in vitro* skin permeation analysis was performed using a franz diffusion cell. In this setup, the egg membrane was a semi-permeable membrane for diffusion. The receptor compartment of the Franz diffusion cell accommodates approximately 60 ml and offers an effective permeation surface area of 3.14 sq. cm. The donor and receptor compartments were separated using an egg membrane. A measured amount of transdermal patch was placed on one side of the membrane.

The receptor medium consists of a pH 5.8 phosphate buffer, and the temperature was maintained at 37±0.5 °C using a water jacket surrounding the receptor compartment. Heat was generated using a magnetic stirrer and thermostatic hot plate. A Teflon-coated magnetic bead inside the diffusion cell agitates the receptor fluid. Throughout the sampling period, samples were extracted and substituted with equivalent volumes of fresh receptor fluid. The withdrawn samples were subjected to spectrophotometric analysis at 227 nm to assess the drug release [8].

Percentage of drug content

The 2 cm^2 area of the transdermal patch was fragmented into smaller segments and placed in a 100 ml volumetric flask. Next, 100 ml of phosphate buffer (pH 7.4) was added to the flask, and the mixture was periodically shaken throughout the day. A suitable dilution was obtained using a phosphate buffer (pH 7.4). A drug-free patch was used to create a blank solution by using a comparable procedure. After filtering the solutions, absorbance was measured at 227 nm [9].

Percentage of absorbed moisture

For three days, film samples of exact weights were placed in a desiccator containing a saturated aluminum chloride solution (79.5% relative humidity) to evaluate their physical stability in high-humidity settings. Subsequently, the films were reweighed, and the percentage of moisture absorption was determined using the relevant formula [10].

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage of moisture lost

To assess the extent of moisture loss from the newly prepared films, accurately weighed samples were placed in a desiccator filled with fused anhydrous calcium chloride for 72 h. After this timeframe, the films were reweighed and the percentage of moisture loss was computed using the following formula [11]:

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Stability study of the optimized formulation

After the designated period, the samples were retrieved, and their physicochemical characteristics were examined. *In vitro*, a diffusion three-month stability assessment was conducted on an optimized patch formulation under controlled conditions of 25±2 °C and 35±2 °C within a humidity chamber set to 75% relative humidity. After the designated period, samples were retrieved and subjected to a thorough examination of physicochemical characteristics and in *vitro* diffusion studies [12].

Drug release kinetics

The drug release profile was assessed for various release kinetics, including zero-order, first-order, Higuchi, and Kores Meyer–Peppas models, to ascertain the drug release mechanism in the developed transdermal patch. The release kinetics was thoroughly analyzed using appropriate statistical methods [13].

RESULTS

Preformulation studies

The organoleptic properties of the product are white and sweet, and it appears as a white crystalline powder.

Melting point

The capillary technique revealed that RXB exhibits a melting point of 228 °C-234 °C, which is consistent with the reference RXB standard.

Solubility studies

Research on RXB solubility has shown that it can dissolve in solvents such as methanol, ethanol, chloroform, DMSO (Di-Methyl Sulfoxide), and DMF (Di-Methyl Formamide). However, it did not dissolve in the distilled water. RXB is moderately soluble in aqueous buffers and has a slight solubility in 0.1N NaOH (Sodium Hydroxide) and acetone.

Table 2: Solubility studies for RXB

Solvent	Inference
Distilled water	Insoluble
Methanol	Soluble
Ethanol	Soluble
0.1N NaOH	Slightly soluble
Acetone	Slightly soluble
Aqueous buffer	Sparingly soluble
Chloroform	Soluble
DMSO	Soluble
DMF	Soluble

Preparation of calibration curve

For the standard stock solution, 10 mg RXB was dissolved in 10 ml of acetone to obtain a concentration of 1000 µg/ml. Working standards were created by diluting this stock solution with phosphate buffer (pH 7.4) and 2% SLS (Sodium Lauryl Sulphate) buffer to achieve concentrations of 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, and 10 µg/ml. This was performed by transferring 1 ml of the stock solution and adjusting the volume with the buffer solution.

Table 3: Absorbance values for RXB

S. No.	Concentration (µg/ml)	Absorbance
1	Blank	0.04
2	2	0.200
3	4	0.317
4	6	0.413
5	8	0.577
6	10	0.706

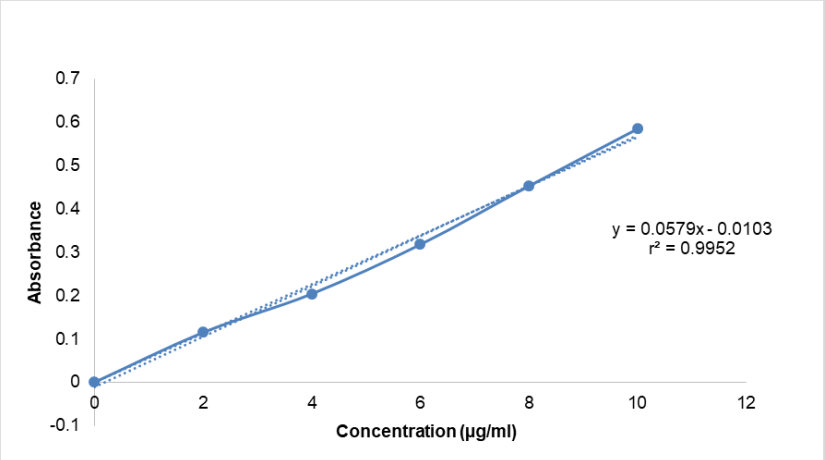

Fig. 3: Calibration curve of RXB

Fourier-transform infrared spectroscopy

Fourier-transform infrared (FT-IR) spectroscopy analysis indicated no evidence of a physicochemical interaction between RXB and the chosen pharmaceutical excipients.

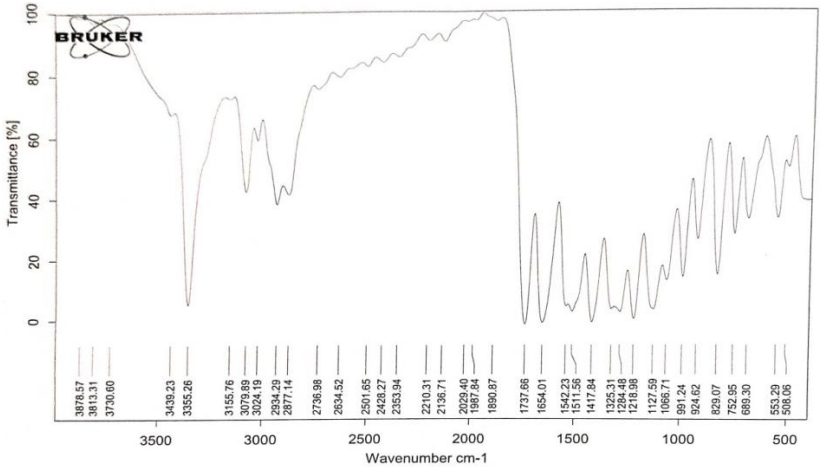

Fig. 4: FTIR spectra of RXB

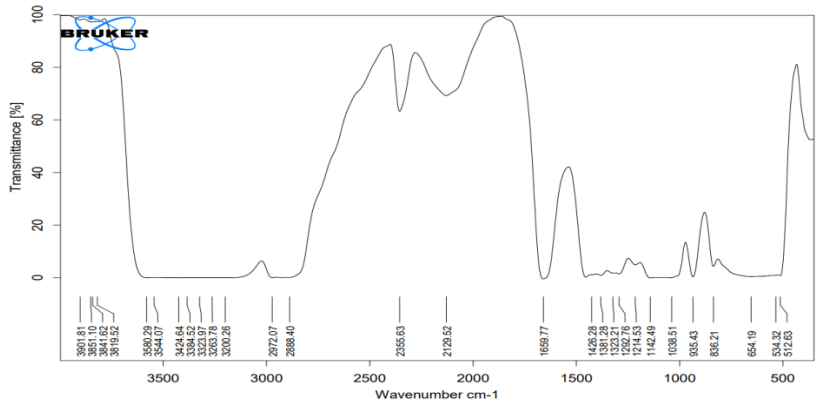

Fig. 5: FTIR spectroscopy of RXB and excipients

Table 4: Reported and observed FT-IR frequencies of pure drug and physical mixture

Functional group	Reported peaks (cm-1)	Observed peaks in pure drug (cm-1)	Observed peaks in the Physical mixture (cm-1)
N-H stretch	3700-3500	3439	3580
Aromatic C-H Stretching	3000-2840	2877	2888
Aromatic C-H Stretching	3000-2840	2934	2972
C=O Stretch	1690-1630	1654	1659
C-O Stretch	1300-1000	1066	1038
C-O Stretch	1300-1000	1127	1142

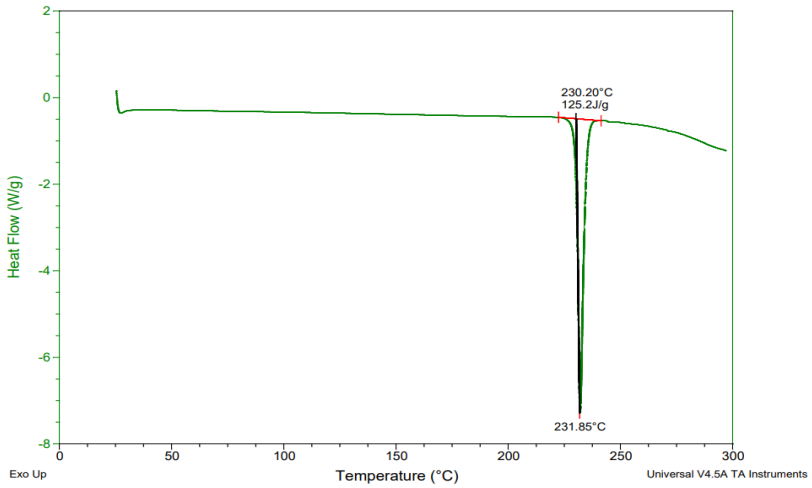

Fig. 6: Thermogram of RXB

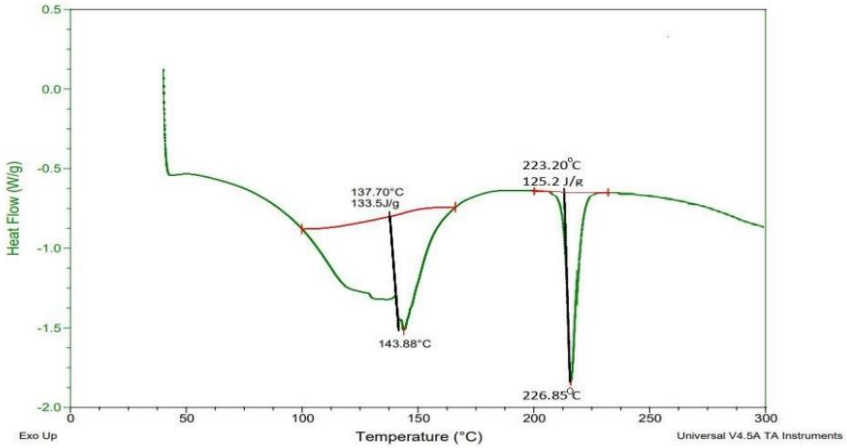

Fig. 7: Thermogram of RXB and excipients

Differential scanning calorimetry (DSC)

A sharp endothermic melting range is seen at 231.85 ˚C in the thermogram of RXB (fig. 6), while a sharp endothermic melting range is shown at 226.85 ˚C and 143.88 ˚C in the thermogram of RXB with excipients (fig. 7). We conclude that there were no chemical interactions between the excipients in the formulations and RXB.

Design of experiments

The developed TDP were subjected to crucial evaluation tests, including thickness assessment, folding endurance, and *in vitro* diffusion studies. These evaluations were performed using the Design of expert (DoE) software version 11.

Response 1 (Thickness)

T=+20.54-0.0875*A-0.0625*B+1.04*C

Analysis of Variance (ANOVA) revealed the results indicated a high significance of the developed linear model, supported by a probability value of<0.05. The coefficient of determination (R^2) was 0.9524, suggesting a robust correlation. The plot of the observed versus predicted T (fig. 8) exhibited a linear relationship, indicating the good predictive capability of the equation. Additionally, the 3D plot (fig. 10) and regression coefficient values of the factors revealed that increasing the amounts of HPMC E50, PVP K30, and PG increased the thickness. Notably, the hydrophilic nature of HPMC E50contributed more significantly to the thickness than did PVP K30 and PG.

Table 5: DoE generated 2^3 factorial design

Run	Factor 1 a: HPMC E50	Factor 2 b: PVP K30	Factor 3 c: PG	*Response 1 (Thickness)	*Response 2 (Folding endurance)	*Response 3 (*in vitro* diffusion studies)
1	1.5	0.3	2	19.7±0.74	58±0.74	52.36±1.36
2	2.5	0.3	2	19.5±0.45	61±0.64	61.42±1.02
3	1.5	0.5	2	19.8±0.27	62±0.55	67.5±1.84
4	2.5	0.5	2	19±0.03	71±0.58	73.26±1.95
5	1.5	0.3	4	21.7±0.31	71±0.54	77.95±1.63
6	2.5	0.3	4	21.5±0.33	82±0.65	83.04±1.74
7	1.5	0.5	4	21.3±0.88	102±0.78	87.06±1.56
8	2.5	0.5	4	21.8±0.30	106±0.54	93.6±1.21

*Mean±SD, n=3

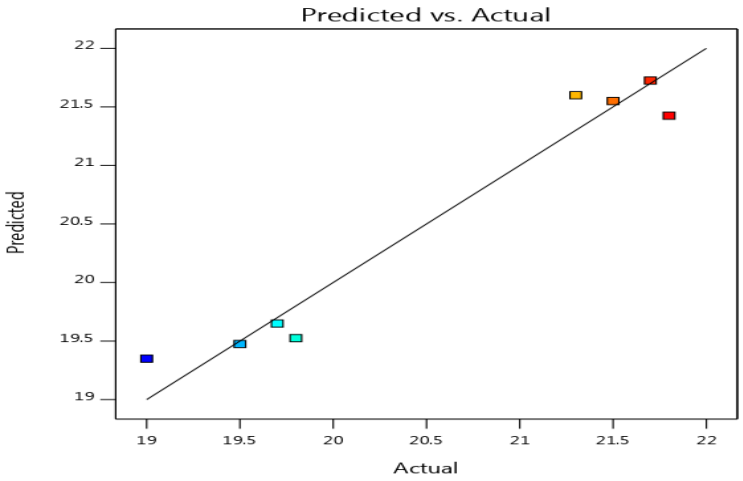

Fig. 8: Predicted vs actual plot for response 1

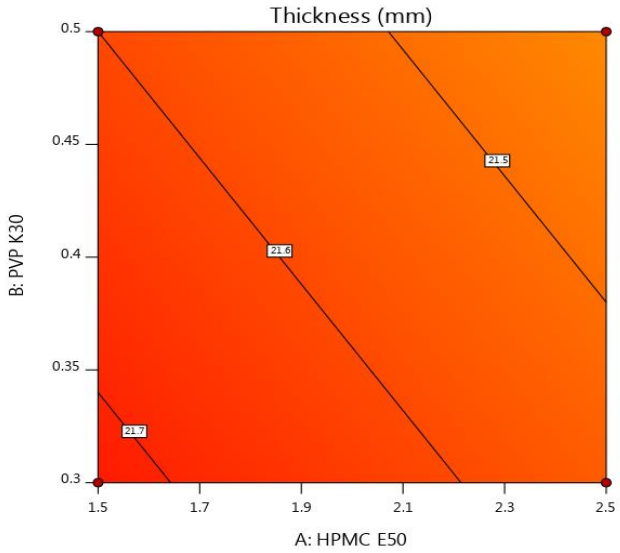

Fig. 9: Counter plot for response 1

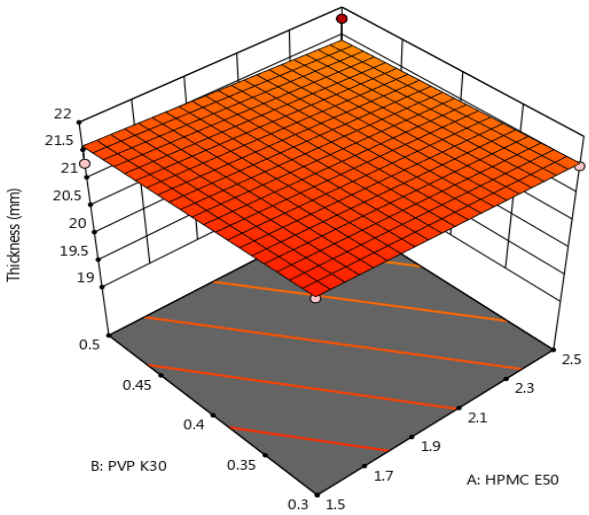

Fig. 10: 3D response surface graph for response 1

Response 2 (Folding endurance)

FE=+76.63+3.37*A+8.63*B+13.63*C

An ANOVA revealed that the developed linear model holds a significant value, with a probability value<0.05. The coefficient of determination (R^2) was computed as 0.9033. The graph depicting the observed folding endurance (FE) against the predicted folding endurance (fig. 11) demonstrates a linear relationship, affirming the robust predictive ability of the equation. Additionally, the examination of the 3D plot (fig. 13), along with the regression coefficient values for the factors revealed a direct correlation between the quantities of HPMC E50, PVP K30, and PG. Significantly, augmenting these components resulted in a proportional increase in the folding endurance. HPMC E50 exhibited the most pronounced effect on folding endurance (FE), which was attributed to its higher solubility than PVP K30 and PG, resulting in more accurate folding endurance values.

Response 3 (*In vitro* diffusion)

ID=+74.52+3.31*A+5.83*B+10.89*C

An ANOVA revealed that the developed linear model holds a significant value, with a probability value<0.05. The coefficient of determination (R^2) was computed as 0.9915, indicating a high level of explanatory capability. The graph illustrating the observed *in vitro* diffusion (ID) versus the predicted *in vitro* diffusion (fig. 14) demonstrates a linear relationship, confirming the robust predictive ability of the equation. Furthermore, analysis of the 3D plot (fig. 16) in conjunction with regression coefficient values for the factors revealed a direct correlation between the quantities of HPMC E50, PVP K30, and PG. Significantly, augmenting these components resulted in a proportional increase in *the in vitro* diffusion. This effect can be attributed to the high viscosity of HPMC E50, which influences the diffusion pathway more significantly than PVP K30 and PG.

Design space

The contour plot for thickness, folding endurance, *and in vitro* diffusion studies depicts the design space for the investigated concentrations of HPMC E50, PVP K30, and PG. The central area of the contour plot, highlighted in yellow, delineated the limits of the design space.

Confirmatory trial

Subsequently, confirmatory checkpoint batches were produced within the acquired design space for validation purposes. The compositions of the formulations for these confirmatory batches are shown in fig. 18.

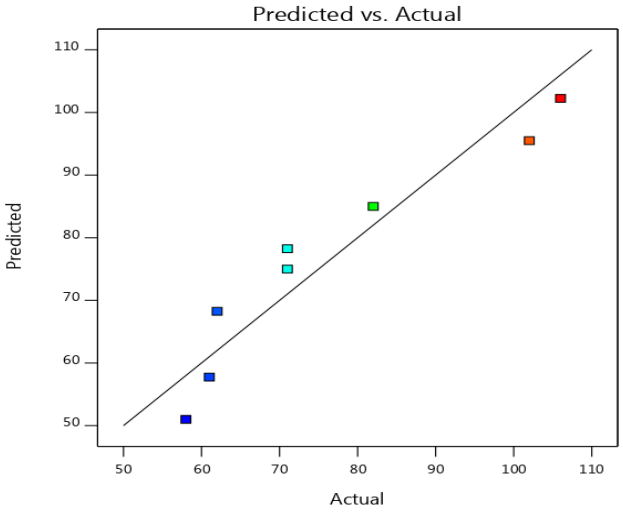

Fig. 11: Predicted vs Actual plot for response 2

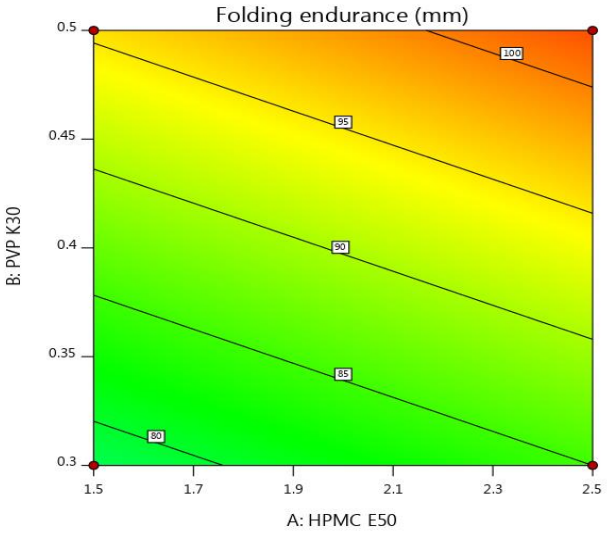

Fig. 12: Contour plot for response 2

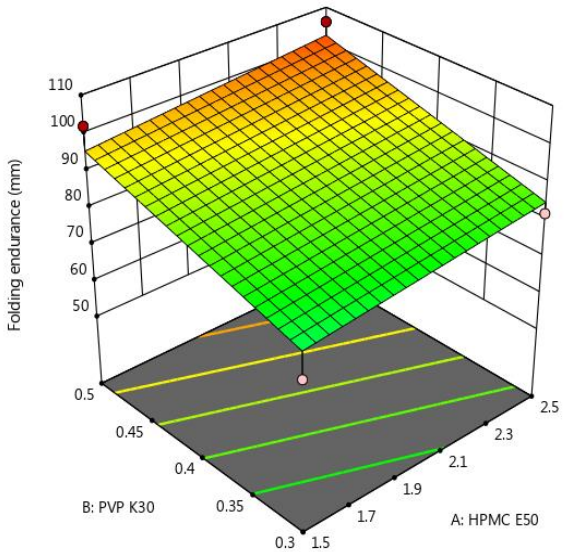

Fig. 13: 3D response surface plot for response 2

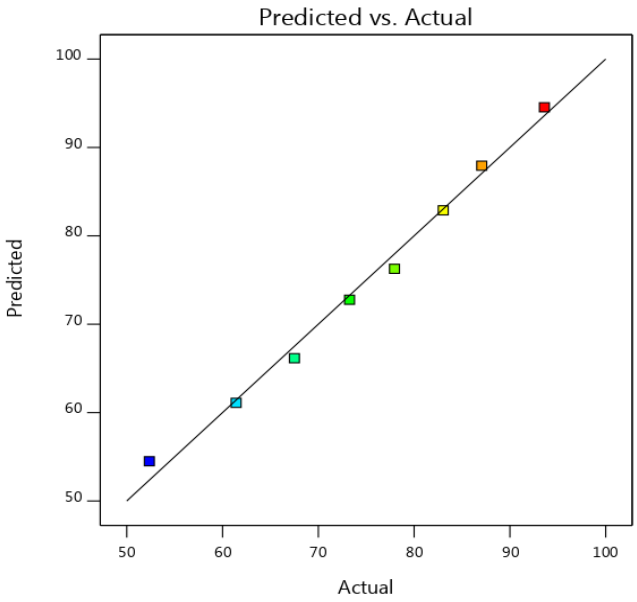

Fig. 14: Predicted vs actual plot for response 3

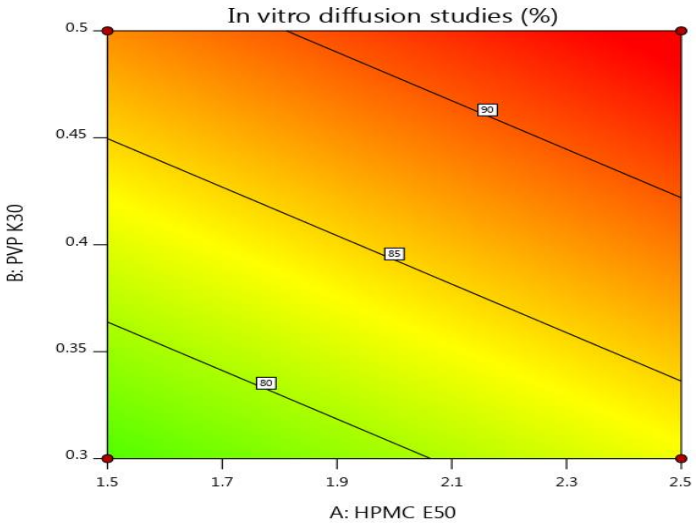

Fig. 15: Contour plot for response 3

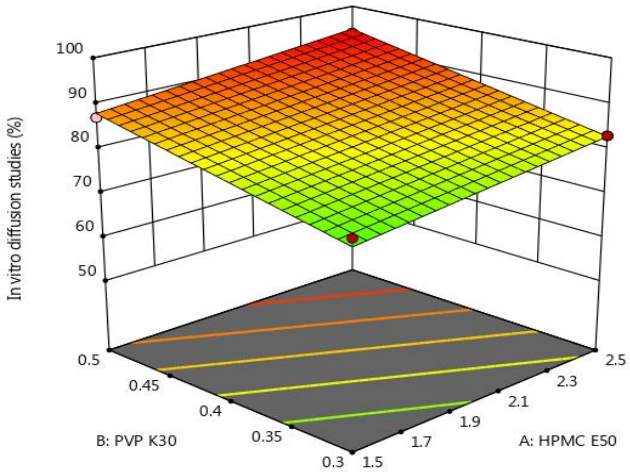

Fig. 16: 3D response surface plot for response 3

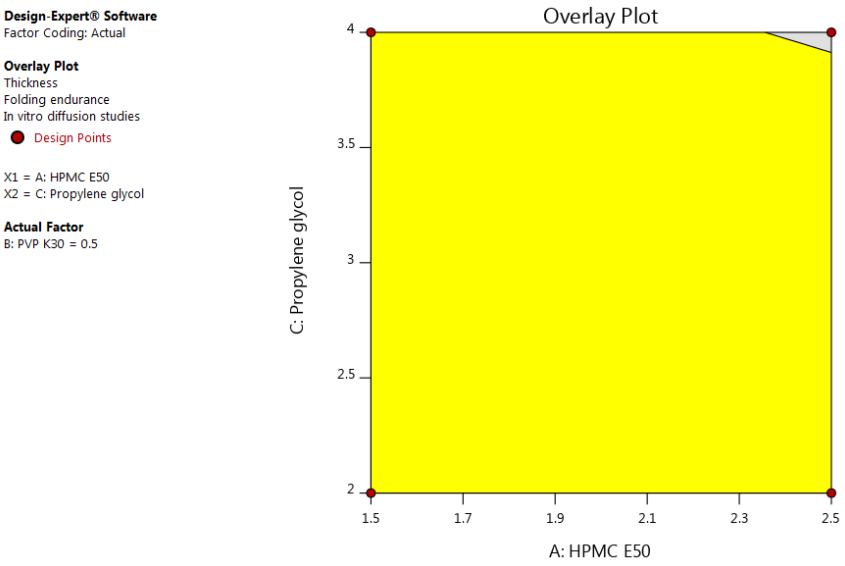

Fig. 17: Design space

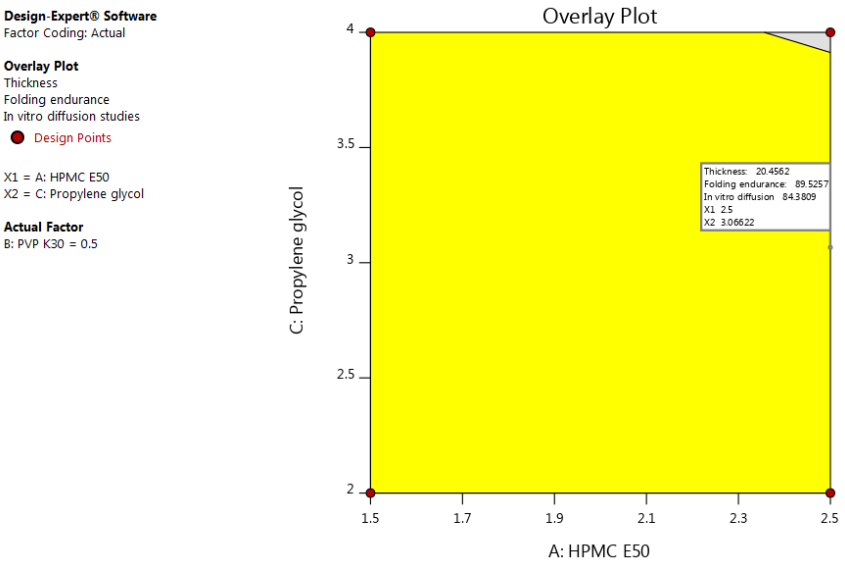

Fig. 18: Overlay plot, by conducting DoE studies on the above eight formulations, the optimized formulation, F9, was obtained

Table 6: Optimized formula

S. No.	Name of pharmaceutical ingredient	F9
1	RXB (mg)	4 mg
2	HPMC E50(g)	2.5g
3	PVP K30(g)	0.5g
4	PG(ml)	3 ml
5	Ethanol(ml)	12 ml
6	Distilled water	Qs

Thickness

The thickness of the optimized formulation was assessed using a digital micrometer. Specifically, the thickness of the optimized formulation (F9) was 0.2913±0.3.

Folding endurance

Repeated folding of the transdermal film was used to evaluate the folding endurance of the optimized formulation. Specifically, the folding endurance of the optimized formulation (F9) was 91±2.

***In vitro* drug release**

The *in vitro* drug release of the optimized formulation was assessed using a diffusion cell apparatus. Specifically, the *in vitro* drug release of the optimized formulation (F9) was measured at 94.58%.

Percent drug content

The percentage of drug content in the optimized formulation was analyzed using a UV-visible spectrophotometer. Specifically, the

percentage of drug content in the optimized formulation (F9) was determined to be 94.26±0.5.

Percentage moisture content

The moisture content of the optimized formulation was assessed by placing the transdermal films in a desiccator. Specifically, the percentage of moisture content in the optimized formulation (F9) was measured at 22.31±0.13%.

Percent moisture lost

The percentage moisture loss of the optimized formulation was determined by placing the TD (Transdermal) film in a desiccator. The percentage of moisture lost from the optimized formulation (F9) was determined to be 1.04%.

Table 7: *In vitro* release of drug

Time (min)	% Drug release*
0	0
60	26.06±0.16
120	37.14±0.27
180	48.53±0.35
240	57.87±0.57
360	69.54±0.52
480	76.08±0.69
720	89.36±0.53
1440	94.58±0.76

Mean±SD, n=3

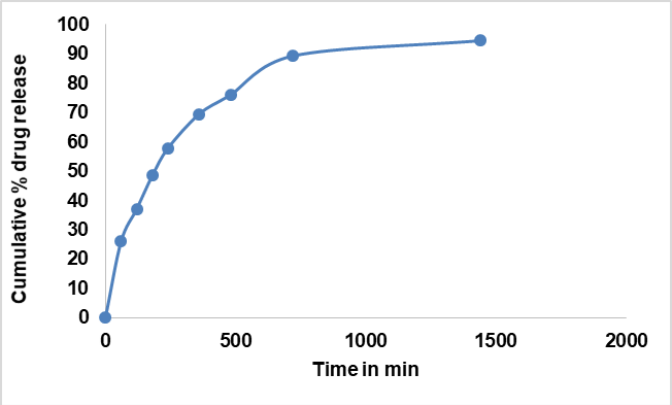

Fig. 19: Drug release studies of TDPs

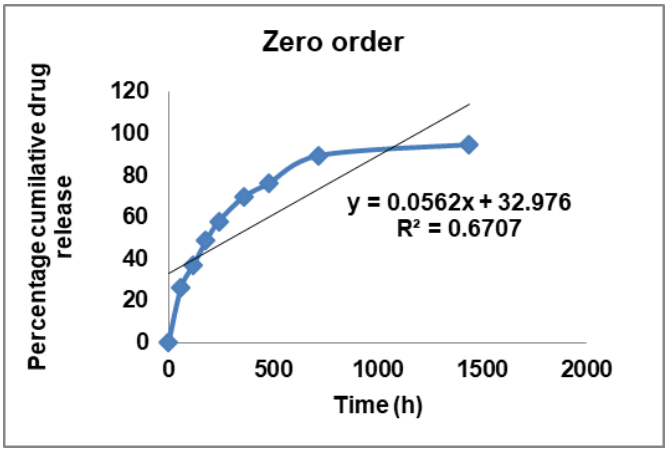

Fig. 20: Zero order kinetics of F9

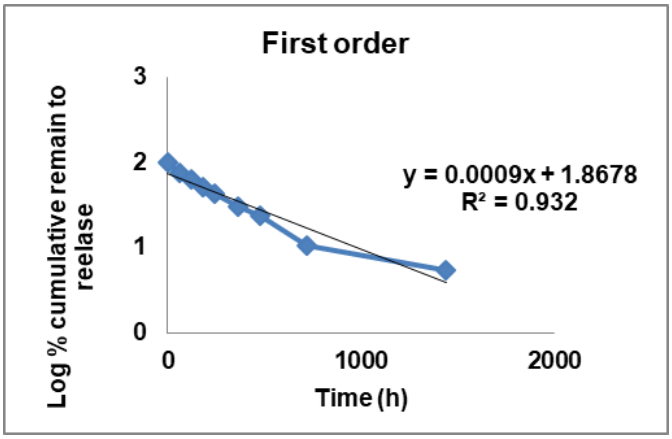

Fig. 21: First-order kinetics of F9

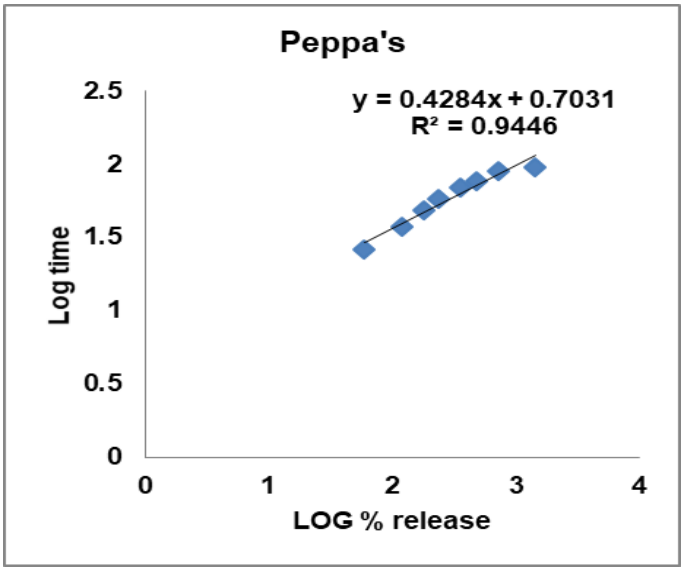

Fig. 22: Korsmeyer-Peppa's graph of F9

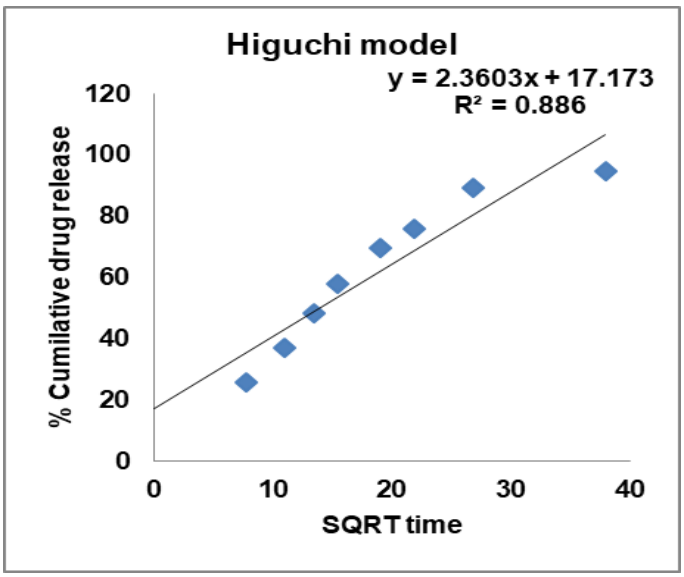

Fig. 23: Higuchi model graph of F9

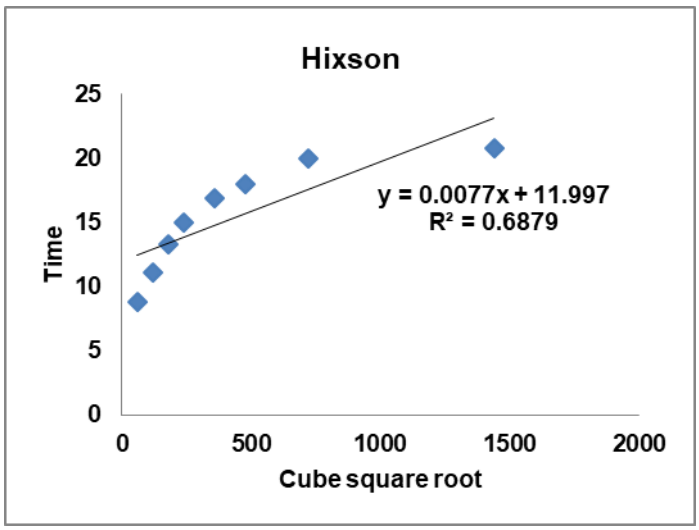

Fig. 24: Hixson graph of F9

The drug release kinetic parameters indicated that the Korsmeyer-Peppas model provided the best fit for the optimized formulation (F9) because it had the highest regression coefficient value (R^2). According to Korsmeyer–Peppas kinetics, the drug was released, resulting in n=0.428. The value of n indicates that the mechanism follows Fickian diffusion.

Table 8: Regression analysis of formulation F9

Formulation code	Zero order r^2	First order r^2	Higuchi r^2	Korsmeyer Peppas r^2	Hixson r^2	'n' value	Best fit model
F9	0.670	0.932	0.914	0.944	0.547	0.428	Peppas

Stability studies of the optimized formulation

It is important to assess the ability of a formulation to determine the stability of drug delivery systems. In a brief stability investigation, we observed the physical and chemical stability of the RXB transdermal patch formulation for three months at room temperature (25±2 °C and 35±2 °C).

Table 9: Stability studies for RXB patches

Time of storage in days	Temperature of storage			
	Percentage drug content 25 °C±2 °C	*In vitro* diffusion studies 25 °C±2 °C	Percentage drug content 35 °C±2 °C	*In vitro* diffusion studies 35 °C±2 °C
0 days	93.26	94.58	94.26	94.58
30 days	92.73	94.86	94.51	94.46
60 days	91.47	93.95	93.18	94.31
90 days	90.26	92.15	93.12	94.06

Mean±SD, n=3

The transdermal patch drug content and *in vitro* diffusion studies were carried out immediately during production and 30 d later for 90 d. Since the drug penetrates the skin more readily around 35 °C-38 °C degrees, it was determined that the transdermal patch remained stable when kept between 35 °C-38 °C.

DISCUSSION

There is a wide selection of TDPs available on the market, each designed to administer different categories of drugs, such as diclofenac sodium, atenolol, aceclofenac, stavudine, pantoprazole sodium, and metoprolol succinate. While aceclofenac and diclofenac patches fall under the category of NSAIDs (Nonsteroidal Anti-Inflammatory Drugs), we developed RXB patches, which are anticoagulants. These patches prevent and treat thromboembolic illnesses, including atrial fibrillation, deep vein thrombosis, and pulmonary embolism [14-16].

Market analysis suggests substantial growth potential for RXB, which is expected to reach US$ 7,995 million by 2023. Projections indicate a CAGR (Compound Annual Growth Rate) of 8.2% from 2024 to 2030, reaching approximately US$ 13970 million. Similarly, the transdermal patch market is expected to experience a CAGR of 4.5% from 2023 to 2029, with revenues increasing from $6.2 billion to $8.0 billion. Recent research has focused on the industry trends within this market. The decision to focus on TDPs stems from their suitability for administration to bedridden patients and individuals allergic to tablets. Such formulations offer direct systemic circulation without first-pass metabolism, thereby minimizing drug metabolism in the liver. PG, chosen as a permeation enhancer due to its compatibility with the log P value of RXB (approximately 1.5), was employed to improve permeation. Previously, RXB was not included in the formulation of the TDPs [17].

The development of RXBTDPs utilized solvent casting guided by a 2^3-factorial design generated using the Design Expert 11 software. Carefully selected dependent variables (thickness, folding endurance, *and in vitro* diffusion) and independent factors are crucial for achieving the desired outcomes. The response surface and overlay plots indicated the creation of the optimal formulation, F9.

FTIR analysis revealed no discernible chemical interactions between the drugs and excipients, with polymers showing no effect on the characteristic bands of the pure drug. DSC comparison of RXB and its physical mixtures showed no interaction, indicating the presence of the drug in its original uniform form [18].

The film thickness and average weight of the formulation F9 were determined using a digital micrometer. HPMC E50's hydrophilic nature increased thickness, whereas PG increased its elasticity. The polymer concentration directly influenced moisture loss. The percentage of drug content fell within the pharmacopeia standards. Increasing the HPMC E50 concentration was correlated with enhanced folding endurance due to its high solubility. *In vitro* diffusion experiments revealed a higher drug release with increased HPMC E50 viscosity, matching Korsmeyer Peppa's kinetics and indicating Fickian diffusion as the release mechanism.

Stability studies conducted at 25±2 °C and 35±2 °C demonstrated better stability and results at higher temperatures. Overall, the results of these tests fell within acceptable limits, confirming the viability of the developed transdermal patch formulation.

CONCLUSION

In conclusion, TDPs containing RXB were fabricated using the solvent casting technique, with formulation F9 identified as the optimized variant. A comprehensive evaluation assessed thickness, folding endurance, drug content, *in vitro* diffusion characteristics, moisture uptake, moisture loss, and stability. The results showed promising outcomes, with the improved formulation achieving approximately 94.58% *in vitro* drug release over 24 h via Fickian diffusion. DSC and FTIR analysis confirmed no significant interactions between the drug and excipients. Each excipient contributed positively to the formulation's efficacy and acceptability. The TDPs ease of administration enhances patient compliance and therapeutic outcomes, offering a convenient topical delivery method for RXB. Further studies are needed to explore the preclinical and clinical activities of these optimized formulations.

Market analysis indicates significant growth for RXB, projected to reach US$ 7,995 million by 2023, with a al Growth Rate (CAGR) of 8.2% from 2024 to 2030, totaling approximately US$ 13,970 million. Similarly, the transdermal patch market is expected to grow at a CAGR of 4.5% from 2023 to 2029, increasing revenue from an estimated $6.2 billion to $8.0 billion. Future research should focus on enhancing drug delivery by understanding the drug's physicochemical properties, skin physiology, enhancer mechanisms, and interactions among formulation components, as the skin offers a safer and more acceptable route for systemic drug administration compared to oral methods.

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AUTHORS CONTRIBUTIONS

All authors played an equal role in this study. P. V. L. N. Priyanka collected the necessary chemicals and reagents for experimental work in our laboratories. Dr. Rama RaoNadendla contributed to the interpretation of the data, and drafted and revised the manuscript to ensure its quality.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

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