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FORMULATION DEVELOPMENT AND EVALUATION OF TRANSDERMAL PATCH OF APIXABAN

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Abstract

The present study focuses on the formulation and evaluation of Apixaban transdermal patches to provide sustained drug release and improve patient compliance. Apixaban, an oral anticoagulant with limited bioavailability due to first-pass metabolism, was incorporated into transdermal patches using the solvent evaporation technique. Various formulations (F1–F6) were prepared by varying polymer concentrations. The patches were evaluated for physicochemical parameters such as thickness, folding endurance, moisture content, tensile strength, drug content, and in-vitro drug release. Among all, formulation F5 demonstrated optimum physical properties and sustained drug release up to 12 hours (98.65%). The drug release followed Higuchi kinetics (R^2 = 0.9874) and Korsmeyer-Peppas model (R^2 = 0.9838), suggesting diffusion-controlled release. Thus, the developed Apixaban transdermal patch offers a promising approach for effective anticoagulant therapy through transdermal delivery.

Keywords: Apixaban, Transdermal patch, Solvent evaporation method, Sustained release, In-vitro drug release, Higuchi model, Korsmeyer-Peppas model, Anticoagulant therapy.

Introduction

Transdermal drug delivery systems (TDDS) have gained significant attention in recent years due to their ability to deliver drugs in a controlled and sustained manner, bypassing the first-pass metabolism and improving patient compliance. These systems offer non-invasive delivery, reduce dosing frequency, and maintain steady plasma drug levels (Prausnitz & Langer, 2008). They are especially beneficial for drugs with short half-lives or poor oral bioavailability.

Apixaban is an oral anticoagulant that selectively inhibits factor Xa, thus preventing the formation of thrombin and thrombus development. It is used for the prevention and treatment of venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE), as well as in stroke prevention in patients with atrial fibrillation (Granger et al., 2011). However, Apixaban has a limited oral bioavailability (~50%) and requires twice-daily administration, which may lead to poor compliance in some patients.

To overcome these limitations, a transdermal delivery approach could be a promising alternative. The transdermal patch of Apixaban can provide a steady release of the drug over an extended period, thereby enhancing therapeutic efficacy and reducing side effects. The formulation of such a patch requires careful selection of polymers, plasticizers, and permeation enhancers to ensure proper drug release, adhesion, and skin permeation.

Several studies have highlighted the success of transdermal patches in delivering cardiovascular and anticoagulant drugs effectively (Bhowmik et al., 2010; Jadhav et al., 2021). The present study aims to develop and evaluate a transdermal patch of Apixaban using suitable polymeric combinations and evaluate its physicochemical properties, drug release profile, and skin permeation characteristics.

Materials and Methods

Material

The formulation development of Apixaban-loaded transdermal patches involved the use of various pharmaceutical-grade chemicals. Apixaban was procured from Bioplus Life

Sciences Pvt. Ltd., Bangalore. Hydroxypropyl methylcellulose (HPMC), used as a film-forming polymer, was obtained from HiMedia Laboratories, Mumbai. Sodium citrate and di-potassium hydrogen orthophosphate, used as buffering agents, were supplied by Loba Chemie Pvt. Ltd. and S. D. Fine Chem. Ltd., respectively. Solvents such as methanol, ethanol, and chloroform required for patch preparation and drug solubilization were sourced from Qualigens Fine Chemicals, Mumbai.

Methods

Preparation of Blank Patches

Accurately weighed combinations of polymers were dissolved in a solvent mixture of chloroform and methanol (1:1 v/v). The resulting solution was poured into a clean glass Petri dish pre-treated with glycerin to facilitate easy film removal. The patches were allowed to dry at room temperature overnight to form blank films.

Preparation of Rate-Controlling Membrane

Rate-controlling membranes were prepared using HPMC K4M, HPMC K15M, and ethyl cellulose (EC). The selected polymers were dissolved in a 1:1 (v/v) mixture of chloroform and methanol, with polyethylene glycol 600 (PEG 600) added as a plasticizer. The homogenous solution was poured into a glass Petri dish and allowed to dry at room temperature for 24 hours to enable solvent evaporation and membrane formation (Lincy et al., 2013).

Preparation of Matrix-Type Transdermal Patches

Matrix-type transdermal patches were prepared using the solvent casting technique. Various combinations of Hydroxypropyl Methylcellulose (HPMC K4M, HPMC K15M) and Ethyl Cellulose (EC) were used as matrix-forming polymers. A fixed quantity of Apixaban (60 mg) and a total polymer weight of 500 mg were accurately weighed and dissolved in 10 mL of chloroform: methanol mixture (1:1 v/v). Polyethylene glycol 400 (PEG 400) was incorporated as a plasticizer. The mixture was vortexed thoroughly to ensure uniformity and then poured into a glass Petri dish previously coated with glycerin to prevent sticking. The films were allowed to dry at room temperature for 24 hours to form clear and flexible transdermal patches.

Table 1: Preparation of matrix type transdermal patches

Formulation Code	Drug (mg)	HPMC K4 (mg)	HPMC K15 (mg)	Ethyl cellulose (mg)	Total polymer weight (mg)	Plasticizer % w/w of total polymer PEG 600 ml	Permeation Enhancer % w/w of total polymer (Methanol, chloroform) ml
F1	60	400	-	100	500	0.5	10
F2	60	300	-	200	500	0.5	10
F3	60	200	-	300	500	0.5	10
F4	60	-	400	100	500	0.5	10
F5	60	-	300	200	500	0.5	10
F6	60	-	200	300	500	0.5	10

*60 mg drug for 12 patches

Evaluation parameters

The prepared transdermal patches were evaluated for the following parameters:

Microscopic evaluation

Representative samples of the prepared transdermal patches were cut and evaluated using an optical microscope (Olympus-Cover-018) in a clean, well-lit laboratory. A Minolta camera was attached to the microscope for image capture. The microscope was calibrated using a standard calibration slide to ensure measurement accuracy. Patch samples were placed on the stage, and the focus and magnification were adjusted for optimal clarity. Surface characteristics such as shape, size, and other visible features were observed and documented. High-quality images were captured under proper lighting conditions (Selvam et al., 2010).

Thickness

The thickness of the transdermal patches was measured using a Vernier caliper. Measurements were taken at three different locations on each patch, and the average

value was calculated. The results were expressed as mean ± standard deviation to ensure accuracy and consistency.

Folding endurance

Folding endurance was determined by repeatedly folding a single patch at the same location until it showed signs of cracking or breakage. The number of times the patch could be folded without breaking was recorded as the folding endurance value.

Tensile strength

A strip measuring 2.5 cm × 2.5 cm was cut from the center of the transdermal patch. The strip was mounted vertically between the upper and lower grips of the tensile strength testing instrument. The device was switched on, and the reading displayed on the screen was recorded. The thickness and breadth of the strip were measured at three different points, and the average values were used for calculations.

Tensile stress (S) was calculated using the formula:

$$S = (m \times g) / (b \times t)$$

Where:

S = tensile stress in 980 dynes/cm^2

m = mass in grams

g = acceleration due to gravity (980 dynes/cm^2)

b = average breadth of the strip in cm

t = average thickness of the strip in cm

Percentage of moisture content

The prepared transdermal patches were individually weighed and placed in desiccators containing activated silica at room temperature for 24 hours. After drying, each patch was reweighed. The percentage moisture content was calculated by determining the difference between the initial and final weights, expressed as a percentage of the initial weight (Izumoto et al., 1992).

Percentage of moisture uptake

Initially, the patches were weighed and placed in a desiccator at room temperature for 24 hours. They were then exposed to 84% relative humidity, maintained using a

saturated solution of potassium chloride in a separate desiccator. After the exposure period, the patches were reweighed. The percentage moisture uptake was calculated as the difference between the final and initial weights, expressed as a percentage of the initial weight.

Drug content analysis

Patches (n = 3) of a specified area (6.16 cm^2) were placed in 10 mL volumetric flasks and dissolved in methanol with the aid of a mechanical shaker. After vortexing, the solutions were filtered, and appropriate dilutions were prepared. The drug content was then analyzed using a UV spectrophotometer at 282 nm.

***In vitro* skin permeation study**

The in vitro skin permeation study was carried out using a Franz diffusion cell with a receptor compartment capacity of 80 mL and an effective diffusion area of 3.14 cm^2. An egg membrane was carefully separated and employed as the semi-permeable barrier for the study. The receptor compartment was filled with 40 mL of phosphate buffer (pH 7.4) to simulate physiological conditions.

The transdermal patch was placed centrally on the egg membrane, which was then mounted between the donor and receptor compartments of the diffusion cell. The donor compartment was positioned so that the membrane just made contact with the surface of the receptor fluid. The entire assembly was maintained on a magnetic stirrer at a constant speed using magnetic beads to ensure uniform mixing.

The temperature of the receptor compartment was maintained at 37 ± 0.5°C throughout the experiment. Samples were withdrawn at predetermined time intervals over a period of 10 hours and analyzed for drug content using a suitable method. After each sampling, the withdrawn volume was immediately replaced with an equal volume of fresh phosphate buffer to maintain sink conditions.

Results and Discussion

The development of transdermal drug delivery systems (TDDS) has garnered significant attention due to its potential to bypass first-pass metabolism, improve patient compliance, and maintain controlled plasma drug levels. In this study, various formulations (F1–F6) of Apixaban transdermal patches were prepared using different

ratios of polymers and plasticizers to evaluate their physicochemical characteristics, mechanical properties, drug content, and drug release behavior.

Table 2 summarizes key parameters such as thickness, folding endurance, moisture content, and moisture uptake. The thickness of patches ranged between 60 μm (F6) to 73 μm (F1), indicating uniformity in formulation and casting technique. F5 showed optimal thickness (65 μm), which is suitable for maintaining flexibility and comfort when applied to the skin. Folding endurance is a crucial mechanical property that determines the ability of a patch to withstand repeated bending without breaking. Among all formulations, F5 demonstrated the highest folding endurance (278), suggesting excellent mechanical strength and flexibility, which are vital for maintaining the patch's integrity during application and movement.

Moisture content (2.05–2.85%) and moisture uptake (3.15–4.58%) were within acceptable ranges across all formulations, reflecting their stability and resistance to microbial growth or brittleness. Notably, F5 had the lowest moisture content (2.05%) and moisture uptake (3.15%), indicating its better stability and lesser hygroscopic nature compared to others.

Mechanical strength and uniformity in drug distribution are critical for effective transdermal patches. Table 3 presents the tensile strength and drug content for all formulations. The tensile strength of the patches varied from 0.845 kg/cm^2 (F3) to 0.995 kg/cm^2 (F6). F5 exhibited a tensile strength of 0.945 kg/cm^2, which is sufficiently high to withstand mechanical stress during handling and use.

In terms of drug content, all formulations showed a high degree of uniformity, ranging between 96.45% and 99.25%. F5 again stood out with the highest drug content of 99.25%, indicating uniform drug dispersion within the polymeric matrix and minimal drug loss during the formulation process.

Table 4 shows the in-vitro drug release profiles for all six formulations over 12 hours. A sustained release pattern was observed in all formulations, which is essential for maintaining therapeutic levels of Apixaban over an extended period. Among them, F5 demonstrated the most controlled and consistent release profile, with 98.65% drug release at 12 hours. The initial burst effect was minimized, and the drug was released in a gradual manner, which aligns well with the goals of a sustained transdermal delivery system.

The drug release kinetics for optimized formulation F5 were studied to understand the mechanism of drug release (Table 5 and Table 6). The data were fitted into various models, including Zero-order, First-order, Higuchi, and Korsmeyer-Peppas. The Higuchi model showed the best fit with R^2 = 0.9874, indicating that the drug release was primarily governed by diffusion through the polymer matrix. The Korsmeyer-Peppas model also showed a high correlation (R^2 = 0.9838), and the release exponent (n) was between 0.5 and 1.0, suggesting an anomalous (non-Fickian) transport, which means both diffusion and polymer relaxation contributed to the drug release. The Zero-order model (R^2 = 0.9745) further suggested a near-constant release rate in later stages, which is desirable in maintaining plasma drug concentrations within the therapeutic window.

Based on the comprehensive analysis of physicochemical properties, mechanical characteristics, drug content, in-vitro drug release, and kinetic modeling, Formulation F5 was selected as the optimized batch. It fulfilled all the criteria of an ideal transdermal patch including acceptable thickness, superior folding endurance, high tensile strength, excellent drug content uniformity, and prolonged, controlled drug release with favorable kinetics. These results support the potential of F5 as an effective transdermal delivery system for Apixaban, offering advantages such as reduced dosing frequency, improved patient adherence, and better therapeutic efficacy in the prevention and treatment of thromboembolic disorders.

Table 2: Thicknesses, folding endurance, % moisture content and % moisture uptake of different formulations of transdermal patch

S. No.	Formulation Code	Thickness (µm)*	Folding Endurance*	% Moisture Content*	% Moisture Uptake*
1.	**F1**	73±5	235±5	2.85±0.45	4.58±0.32
2.	**F2**	70±8	240±8	2.74±0.85	3.65±0.45
3.	**F3**	69±4	255±6	2.36±0.74	3.85±0.69
4.	**F4**	70±6	255±7	2.85±0.69	4.25±0.85
5.	**F5**	65±4	278±5	2.05±0.55	3.15±0.74
6.	**F6**	60±6	245±6	2.85±0.85	3.78±0.12

*Average of three determinations (n=3±SD)

Table 3: Tensile strength and drug content analysis of different formulations

S. No.	Formulation code	Tensile Strength (kg/cm^2)	% Drug Content
1.	F1	0.891±0.085	96.85±0.15
2.	F2	0.865±0.074	97.74±0.36
3.	F3	0.845±0.065	98.45±0.45
4.	F4	0.969±0.074	96.45±0.36
5.	F5	0.945±0.063	99.25±0.74
6.	F6	0.995±0.074	97.88±0.65

Table 4: *In vitro* % Permeation Profile of Apixaban in Formulation F1-F6

Time	% of Drug Release					
(hr)	F1	F2	F3	F4	F5	F6
0.5	34.45	32.25	28.85	29.98	25.65	23.15
1.0	46.65	42.65	36.65	38.85	38.85	35.45
2.0	59.98	55.47	48.98	55.65	46.65	42.23
4.0	68.85	69.98	63.32	67.74	55.98	53.32
6.0	78.98	82.23	78.98	76.65	69.98	65.47
8.0	89.95	92.25	88.85	89.95	76.58	74.45
10.0	98.12	96.65	98.78	98.85	88.85	88.12
12.0	99.15	98.78	99.05	99.08	98.65	94.45

Table 5: *In-vitro* drug release data for optimized formulation F5

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	0.301	25.65	1.409	74.35	1.871

1	1	0	38.85	1.589	61.15	1.786
2	1.414	0.301	46.65	1.669	53.35	1.727
4	2	0.602	55.98	1.748	44.02	1.644
6	2.449	0.778	69.98	1.845	30.02	1.477
8	2.828	0.903	76.58	1.884	23.42	1.370
10	3.162	1	88.85	1.949	11.15	1.047
12	3.464	1.079	98.65	1.994	1.35	0.130

Table 6: Regression analysis data of Apixaban loaded Transdermal patches

Batch	**Zero Order**	**First Order**	**Higuchi order**	**Korsmeyer peppas**
	R^2	**R^2**	**R^2**	**R^2**
F5	0.9745	0.8184	0.9874	0.9838

Conclusion

The study successfully formulated Apixaban transdermal patches using the solvent evaporation method. Among all, formulation F5 showed the best results with good physical properties, uniform drug content, and sustained drug release up to 12 hours (98.65%). Drug release followed Higuchi kinetics with non-Fickian diffusion, indicating a controlled release system. These patches offer a promising alternative to oral delivery, improving patient compliance and therapeutic effectiveness.

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