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EVALUATION OF ANTIRETROVIRAL TDDS CONTAINING NATURAL PENETRATION ENHANCER

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Keywords:

Transdermal drug delivery system, Natural permeation enhancer, HPMCK15M, PVPK30, and EC

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ABSTRACT: Aim: This study aims to explore the potential of transdermal drug administration as a viable alternative to conventional medication delivery systems. Specifically, the focus is on the development and evaluation of transdermal patches containing Lamivudine and Stavudine for the treatment of AIDS. The overarching objectives include extending drug release duration, reducing administration frequency, and enhancing patient compliance. **Material & Methods:** The formulations under investigation are meticulously designed using a combination of HPMCK15M, PVPK30, and EC in varying ratios. The patches are subjected to a thorough assessment, encompassing critical parameters such as film thickness, tensile strength, and drug content homogeneity. The incorporation of Tween 80 and dimethyl sulfoxide as plasticizer and penetration enhancer is a key methodological consideration for optimizing the transdermal patches. Additionally, the study explores the impact of natural permeation enhancers, such as oleic acid, eucalyptus oil, and clove oil, on drug permeation and release kinetics. **Results:** The outcomes of the study reveal promising findings, with the transdermal patches exhibiting favorable characteristics, including optimal film thickness, tensile strength, and uniform drug content. The use of Tween 80 and dimethyl sulfoxide as plasticizer and penetration enhancer proves effective in enhancing patch properties. Furthermore, the incorporation of natural permeation enhancers demonstrates a significant impact on drug permeation, with a notable achievement of zero-order kinetics in drug release. These results underscore the potential of transdermal drug delivery to address limitations associated with traditional dosage forms, offering a novel and promising approach for enhanced bioavailability and improved patient outcomes in the context of AIDS treatment.

INTRODUCTION: A transdermal drug delivery system (TDDS) refers to the application of medications in the form of self- contained patches directly onto the skin [1]. These patches are designed to release the drug through the skin and into the systemic circulation at a predetermined and controlled rate [2].

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The primary objective of TDDS is to enhance therapeutic efficacy while minimizing drug side effects. By sustaining a consistent drug concentration within the therapeutic window over an extended period, TDDS aims to prevent levels from dropping below the minimum effective concentration or rising above the maximum effective concentration.

This approach ensures a more prolonged and controlled delivery of the drug, contributing to improved treatment outcomes [3]. In response to the limitations of conventional medication delivery systems, transdermal drug administration has emerged as a promising avenue [4, 5], aiming to

extend drug release duration, decrease administration frequency, and bolster patient compliance [6]. This study delves into the development and evaluation of transdermal patches containing Lamivudine and Stavudine for AIDS treatment. Lamivudine is a potent nucleoside analog reverse transcriptase inhibitor (nRTI). Lamivudine is a cytidine analogue. It blocks hepatitis B virus reverse transcriptase in addition to blocking HIV reverse transcriptase types 1 and 2 [7]. Stavudine is an analog of thymidine. Stavudine triphosphate works by decreasing mitochondrial DNA synthesis and blocking the cellular DNA polymerases [8]. Meticulously crafted formulations, incorporating HPMCK15M [9], PVPK30, and EC [10] in varying proportions, were subjected to a comprehensive assessment encompassing film thickness, tensile strength, and drug content homogeneity. The effective utilization of Tween 80 and dimethyl sulfoxide as plasticizer and penetration enhancer underscored the optimization of these patches, presenting a viable alternative to traditional delivery methods [11, 12].

The study outcomes underscore the potential of transdermal drug delivery to revolutionize AIDS treatment, offering a novel approach to enhance bioavailability and mitigate adverse effects. The carefully selected natural permeation enhancers, such as oleic acid, eucalyptus oil, and clove oil, demonstrated considerable promise in augmenting drug permeation [13, 14]. Furthermore, the incorporation of these enhancers in the transdermal matrix showcased zero-order kinetics in drug release, emphasizing sustained and controlled delivery. The study's findings not only shed light on the effectiveness of the transdermal therapeutic system but also highlight its potential to address critical challenges associated with traditional dosage forms, presenting a significant step forward in optimizing drug delivery for improved therapeutic outcomes.

MATERIALS AND METHODS: The acquired medication sample underwent solubility testing, identification, and compatibility testing as part of the preformulation process. The drug's melting point was measured using a melting point device. To ascertain the material's melting point, we used a digital melting point instrument. The capillary was then placed in the digital melting point device with the desired quantity of material. As soon as the target temperature is attained, the sample's M.P. The ice was melting. Books were taken into account. We have tracked the next three readings and compared their average value to the standard.

Analysis of Solubility: In order to dissolve the appropriate medication sample, a solubility assay was done prior to formulation. We had researched the medication product's solubility study using a literature review and references to the Pharmacopeia. λMax 82 Determined We scanned for maximal absorbance in the UV bands from 190 to 380 nm after dissolving Lamivudine and Stavudine in a combined solution of Methanol: water (1:10). The greatest absorbance of lamivudine was observed at 270 nm, whereas that of stavudine was seen at 263 nm. The Making of the 83rd Standard Curve and the Buffering Process pH 1.2 buffer acid.

In a 200 ml flask, we mixed 50 ml of 0.2M Kcl, 85 ml of 0.2N NaoH, and DW to create a buffer. pH testing revealed a range of 1.2 to 0.1. Acid-base buffer, 7.4 phosphate. The buffer was prepared by adding DW to a 100 ml flask containing 25 ml of 0.2M potassium dihydrogen orthophosphate solution and 19.55 ml of 0.2N NaoH solution. The pH level was determined to be 7.4 0.1.

An Initial Stock Solution for pH 1.2 Acidic Buffer: Lamivudine and Stavudine, each 100 mg, were dissolved in 10 ml of MeoH in 100 ml flasks. Concentrate a 1000 mg/ml solution to 100 ml by adding buffer (pH 1.2). For the acidic buffer (pH 1.2) secondary stock standard solution, 10 ml was transferred to a 100 ml volumetric flask from the stock solution, and the remaining volume was made up with pH 1.2 buffers to achieve a concentration of IR 100 g/ml. Phosphate buffer (pH 7.4) primary stock solution: To get a solution of 1000 g/ml con, I dissolved 100 mg of pharmaceuticals in 10 ml of MeoH in 100 ml of flasks and brought the volume up to 100ml with pH 7.4 PBS. To get a concentration of 100 g/ml, a secondary stock solution of phosphate buffer (pH 7.4) was prepared by placing 10 ml from the stock solution into a 100 ml flask and making up the volume with pH 7.4 buffer. Several concentrations, from 2-12 g/ml, were produced. At 263 nm and 270 nm, the

absorbance of each solution was determined. A graph of concentration vs absorbance was drawn.

Analysis of Compatibility: The FTIR analysis approach was chosen and carried out to investigate the compounds' compatibility with each other and the polymer blend. Shimadzu and ATR spectrophotometers were used to scan Lamivudine and Stavudine pharmaceuticals, natural permeation enhancers & polymers (HPMCK15M, PVPK30, and EC), and combination mixtures of medications and polymer for changes in functional group or location. When using the transdermal administration technique, the recommended daily dosage of Lamivudine is 150 mg. When taken orally twice day, the recommended daily dosage of Lamivudine is 300 milligrams (mg). The amount of lamivudine needed to create a once-daily patch is 300 mg.

The therapeutic system dosage would be half that of oral administration because of first-pass metabolism. Hence, if you need to take 150 mg of the medicine, divide 300 by 2 and you get that number. Take 30 milligrams of stavudine twice day. When used orally, the recommended daily dosage of Stavudine is 60 milligrams. It has been estimated that 60 mg of medication should be put into a patch for once day use. Half of the oral dosage would be used in a therapeutic setting. Hence, if you need to take the medicine, you'll need to take 30 mg (60 minus 2). Products for transdermal application the solution casting method was used to create the patches in the years 84–92. The transdermal patch was made by combining HPMCK15M, PVPK30, and Ethyl Cellulose in a number of different ratios. The polymers were weighed out and dissolved in a suitable solvent before being combined with a magnetic stirrer untila clear solution formed. The pharmaceuticals were then added and the mixture was put in an ultra sonicator bath machine (Elmasonic S150) for 30 minutes to ensure thorough dissolution. To make the patches, the polymer solution was poured into bangles and then let it dry for 24 hours at room temperature in a dust-free area. To slow the rate at which the solvent evaporated, an inverted funnel was placed over the bracelets. The 3.14 patches were cut and packaged in aluminum foil before being stored in a desiccators.

RESULT & DISCUSSION:

Evaluation of Formulated Transdermal Patches:

FTIR Studies for Transdermal Patches: To measure the drug polymer interaction, FTIR analyses were carried out. The interaction between the medication and polymer was examined by means of a compatibility study. The FTIR spectra was analyzed between 4000 and 4000 cm-1 in wave number. The peaks of the medication lamivudine are not uniform.

C-H stretching at 2960

N-C stretching at 2837 & 2732,

C=N at 1650 and C–H stretching at 2960, O–H stretching at 3587,

Aromatic C=C at 1496,

Aromatic C-N at 1087 & 1317 cm–1

The issue of Lamivudine's purity has been resolved. If no drug-polymer interaction has taken place, the FT-IR spectra of the formulations should show similar peaks. The transdermal patch spectra also show the characteristic peak of pure lamivudine.

Stavudine Medication Also shown: N–H stretching at 2882.5 cm-1and at 3169.5 cm-1 and. Sharp peak of aromatic C=O Stretching structure at 1694.3 cm^{-1}.Similar, indistinguishable peaks are observed in drug-loaded polymeric Transdermal patches comprised of hydroxypropyl methyl cellulose, ethyl cellulose, polyethylene glycol, and polyvinyl pyrrolidone. Hence, the combination of polymer and medication was not recognized to result in any change or cooperation. The medicine has not undergone any chemical changes and is now available for use.

TABLE 1: FORMULATION OF TRANSDERMAL PATCHES WITH NATURAL PERMEATION ENHANCERS

Formulation	Drug		HPMC K15M (mg)	EC (mg)	PVPK30 (mg)	Solvent (DCM/ Methanol) (ml)	PEG-400 (ml)	Natural Permeation Enhancer
	Lamivudine	Stavudine						
								2:4 (Oleic acid &

FP1	150	30	50	100	250	5	2	Eucalyptusoil)
FP2	150	30	50	100	250	5	2	2:4 (Oleic acid & Menthol)
FP3	150	30	50	100	250	5	2	2:4 (Oleic acid & Clove oil)
FP4	150	30	50	100	250	5	2	2:2:2 (Oleic acid, Eucalyptus oil& Menthol)

Preformulation Studies: Appearance and colour of drug Stavudine comes in a white to yellowish powder form, whereas Lamivudine is a white powder.

Melting Point: Lamivudine has a melting point of 176°C, whereas stavudine's is 165°C.

Solubility: The medication is highly soluble in DW, but only mildly soluble in acetonitrile, MeoH, and dichloromethane and ethanol. It dissolves well in dichloromethane, ethanol, and acetone but very minimally in methanol and acetonitrile and at all in water.

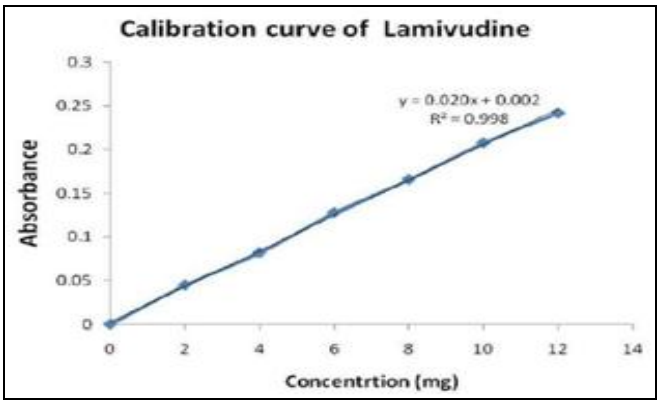

FIG. 1: LAMIVUDINE DRUG STANDARD CURVE AT 270 NM USING PHOSPHATE BUFFER 1.2 pH

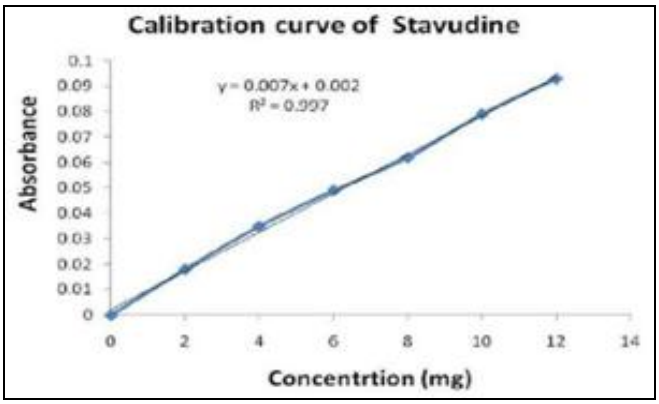

FIG. 2: STAVUDINE DRUG STANDARD CURVE AT 263 NM USING BUFFER 1.2 pH

Physicochemical Evaluation: Several metrics from the physicochemical tests of Transdermal Patches of Stavudine and Lamivudine with Natural Permeation enhancer were presented in the tables, including the percentage of moisture lost, the homogeneity of the drug content, the percentage of moisture absorbed, the thickness, and the folding endurance.

TABLE 2: PHYSICAL AND CHEMICAL EVALUATION DATA OF TRANSDERMAL PATCHES OF STAVUDINE AND LAMIVUDINE WITH NATURAL PERMEATION ENHANCER

Formulation code	% Drug Content		Folding endurance	Tensile strength Kg/mm2	Thickness (mm)	Weig ht variat ion(mg)
	Lamivudine	Stavudine				
FP1	98.64±3.32	95.92±3.32	56±12.04	0.33±0.008	0.150±0.03	3.56±0.81
FP2	97.62±3.14	98.59±3. 14	57.4±21.0	0.38±0.03	0.151±0.004	3.69±0.80
FP3	98.51±2.17	98.61±2.18	59±18.20	0.33±0.08	0.153±0.030	3.59±0.70
FP5	99.25±2.42	98.71±1.43	59±24.33	0.36±0.008	0.151±0.021	3.83±1.80
FP5	98.52±1.42	97.51±2.17	60±10.41	0.35±0.001	0.152±0.014	3.75±1.84
FP6	99.55±2.42	99.65±2.42	61±22.03	0.34±0.08	0.150±0.015	4.15 ±1.84

TABLE 3: PHYSICOCHEMICAL EVALUATION DATA OF TRANSDERMAL PATCHES OF STAVUDINE AND LAMIVUDINE CONTAINING NATURAL PERMEATION ENHANCER

Formulation code	Moisture Content %	Moisture uptake %	Swelling index	Elongation %
FP1	2.92±0.35	4.77±3.13	22.22±1.38	27.23±2.51
FP2	2.83±0.77	4.57±3.7	23.83±0.72	27.10±2.12
FP3	2.89±1.29	4.42±1.22	22.49±2.12	27.65±2.61
FP4	3.12±1.82	4.62±0.85	22.39±0.74	27.71±4.12
FP5	3.13±0.98	4.45±1.06	23.25±1.37	27.02±4.19
FP6	3.45±2.78	4.5±1.45	22.15±1.25	28.14±4.71

TABLE 4: *IN-VITRO* DRUG PERMEATION OF DRUG -LAMIVUDINE KINETICS

Time (hrs)	FP1	FP2	FP3	FP4	FP5	FP6	FP7
1	26.26	8.23	7.92	9.01	10.21	12.9	8.23
2	44.62	15.19	13.28	15.02	18.8	18.4	14.99
3	58.62	28.86	25.81	28.97	30.95	28.4	26.98
4	66.88	37.07	35.67	34.87	41.26	40.1	35.42
5	76.61	47.85	42.82	44.01	49.85	49.8	43.22
6	81.52	54.88	53.34	54.76	55.76	56.87	50.76
8	89.75	60.02	59.12	62.02	63.02	65.4	55.69
10	94.45	65.03	61.35	67.34	70.78	71.56	58.56
12	99.02	67.98	62.21	70.17	72.14	73.2	61.21

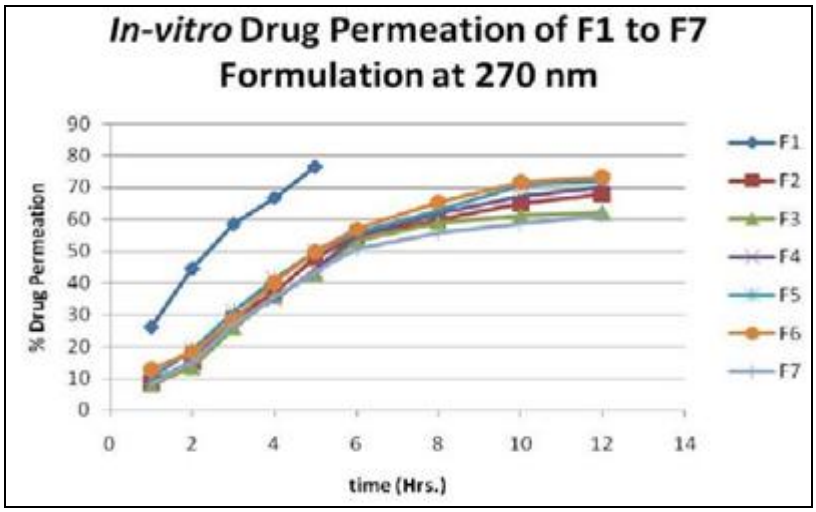

FIG. 3: *IN-VITRO* DRUG PERMEATION OF LAMIVUDINE DRUG

TABLE 5: *IN-VITRO* DRUG PERMEATION OF STAVUDINE KINETICS

Time (hrs)	FP1	FP2	FP3	FP4	FP5	FP6
1	7.83	7.55	8.93	9.01	8.12	9.3
2	14.59	11.98	15.14	15.29	13.02	16.1
3	23.81	22.28	24.12	29.02	25.20	32.25
4	31.52	31.02	35.21	34.01	31.02	39.16
5	45.14	40.12	42.01	49.12	46.94	47.08
6	55.03	49.79	55.73	57.42	56.22	60.52
8	62.21	61.46	66.84	68.96	62.01	71.62
10	70.66	68.11	75.82	79.88	72.43	85.61
12	83.52	75.44	80.82	92.88	85.71	94.71

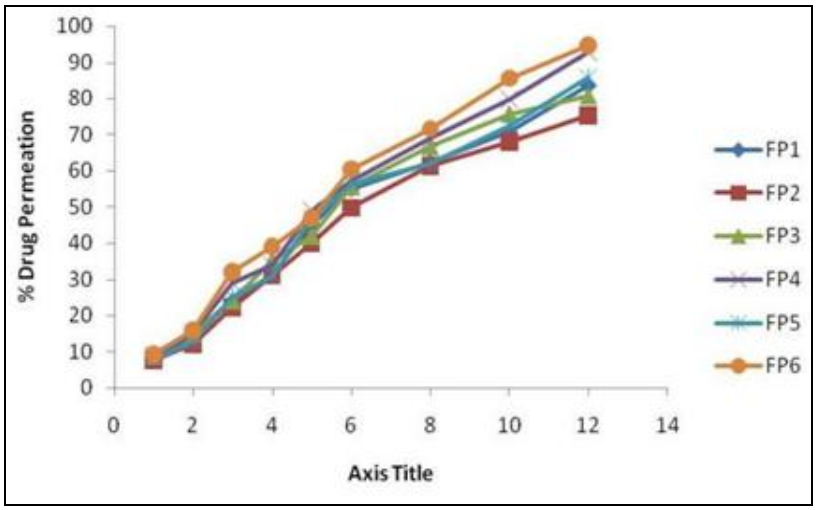

FIG. 4: *IN-VITRO* DRUG PERMEATION OF STAVUDINE OF FP1 TO FP6

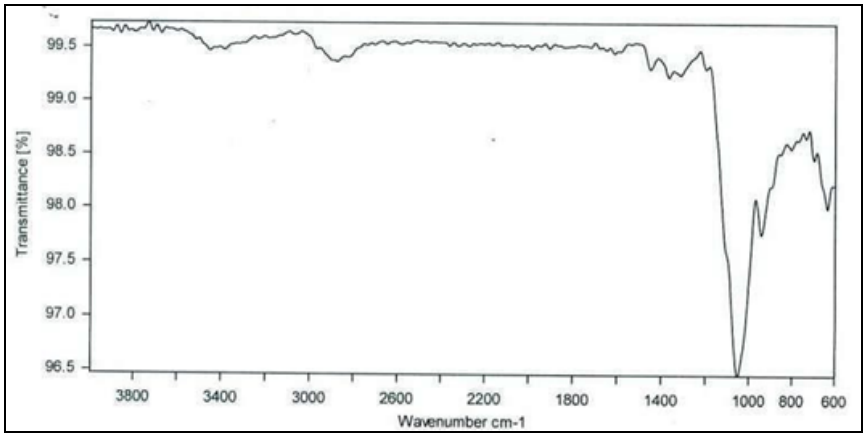

FIG. 5: FTIR SPECTRA OF HPMC K15M

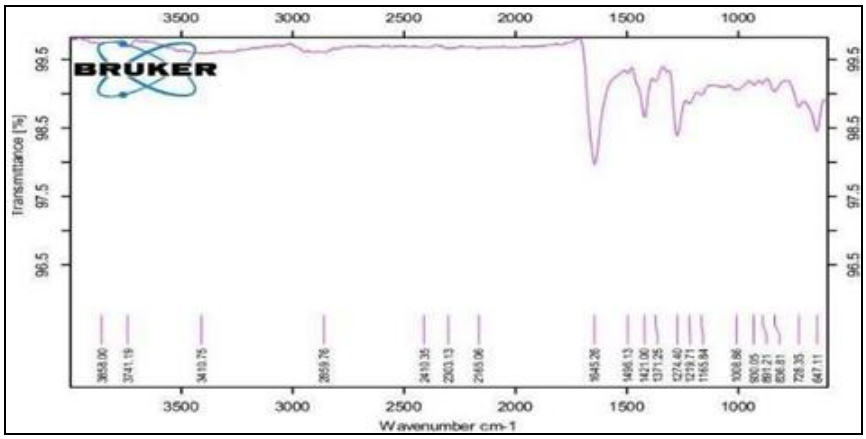

FIG. 6: FTIR SPECTRA OF POLYVINYL PYROLIDONE K30

Stability Study: For stability experiments in accordance with ICH recommendations, FP6 was subjected to 250 degrees Celsius and 60 Percentage relative humidity (RH), 400 degrees Celsius and 75 Percentage RH, and these conditions were monitored for three months. No measurable increase in adaptability was found, however there was a modest shift in several physical and chemical assessment parameters **Table 7**. The stability of a drug product is a key factor in preserving its effectiveness, quality, and safety. If it turns out that the formulation is unstable, it will have an effect on the physical and chemical characteristics.

TABLE 6: STABILITY STUDY OF FP6

S. no.	Evaluation Parameter	At 0 day	After 90 days
1	Thickness (mm)	0.34±0.008	0.33 ± 0.06
2	Weight variation	0.150±0.011	0.152 ± 0.011
3	Percentage Drug Content of Lamivudine	99.55±2.42	98.82 ± 1.25
4	Percentage Drug Content of Stavudine	99.65±2.42	98.91 ± 1.22
5	Folding endurance	61±22.03	60 ± 23.23
6	Tensile Strength Kg/mm2	4.15±1.84	3.99±1.80
7	Percentage Elongation	28.14±4.71	27.94 ± 4.12
8	Percentage Moisture content	3.45±2.78	3.33 ± 0.94
9	Percentage Moisture uptake	4.5±1.45	4.5 ± 3.03
10	Swelling index	22.15±0.74	22.34 ± 0.71

Skin Irritation Test: Albino rats were used to study the skin irritation test for improved formulation. As no adverse effects, such swelling or redness, were seen, it was determined that the formulation was safe for topical use.

TABLE 7: SKIN IRRITATION STUDY OF OPTIMIZED FORMULATION

Normal	FP%: Drug	Blank Film	Formalin
-	-	-	++**

Erythema	Edema
- Nil	- Nil
+ Mild	* Mild
++ Severe	** Severe
+++ Very severe	*** Very severe

CONCLUSION: In conclusion, transdermal drug administration offers a promising alternative to conventional dose medication delivery systems, overcoming limitations by aiming to extend medication release duration, decrease administration frequency, and enhance patient compliance. This study focused on the development and evaluation of transdermal patches containing Lamivudine and Stavudine for AIDS treatment. The patches, composed of HPMCK15M, PVPK30, and EC in varying ratios, demonstrated favorable characteristics such as film thickness, tensile strength, and drug content homogeneity. Utilizing Tween 80 and dimethyl sulfoxide as plasticizer and penetration enhancer proved effective. Formulation F6, incorporating natural permeation enhancers, exhibited significant drug release, and a combination of oleic acid, eucalyptus oil, and clove oil in a 2:2:2 ratio showed promise. Pharmacokinetics revealed enhanced drug permeation with natural enhancers, and zero-order kinetics governed drug release. PVP and EC concentrations influenced patch moisture content, with PVP concentration affecting release rate and EC concentration ensuring sustained delivery. Skin irritation tests and stability analysis on the final formulation indicated safety and stability. Overall, this transdermal therapeutic system demonstrates potential for improved bioavailability and reduced adverse effects.

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