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RESEARCH ARTICLE

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Effect of hydrophilic and hydrophobic polymer on the release of ketoprofen and allopurinol from bilayer matrix transdermal patch

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Abstract

The aim of this study was to design a matrix transdermal patch of ketoprofen and allopurinol for the possible treatment of arthritis with reduced side effects. For this purpose, a bilayer matrix transdermal patch was prepared with an immediate release layer of Methocel containing ketoprofen while secondary sustained layer composed of allopurinol with combinations of Eudragit RL100 and Methocel. The patch was studied for swelling index in distilled water and was found to increase with an increase in concentration of hydrophilic polymer. The in vitro dissolution was conducted in USP dissolution apparatus II using phosphate buffer saline (pH 7.4) as dissolution medium at 37 ± 2°C. Based on in vitro dissolution studies, $KA1_{BL}$ (99.65% release in 10 hr) was selected for ex vivo permeation studies through Franz diffusion cell using excised abdominal skin of albino rats, and using clove oil and menthol as permeation enhancers. The optimized formulation $KA1_{BL}$-M_3 released 69.37% drug over 12 hr and followed zero-order kinetics with anomalous release mechanism. The patch had uniform distribution of components as per digital microscopic analysis.

KEYWORDS

bilayer matrix patch, clove oil, Eudragit RL100, kinetics, menthol, methocel

1 | INTRODUCTION

For local and systemic drug delivery, transdermal route has been widely studied as the potential route of drug administration.[1] When the skin is employed as the route of drug administration, it is known as transdermal administration and the systems used for delivery of drugs are called transdermal therapeutic systems or transdermal patches. This dosage form is designed to noninvasively administer the effective therapeutic concentration of active pharmaceutical ingredients through the skin medium at a controlled and predetermined rate over an extended time period and to maintain a sustained action for a constant plasma level and concentration of the drugs.[2] Transdermal drug delivery system (TDDS) is a potentially efficient option for delivering regular and specified doses of drugs which is convenient and painless.[3] It is an efficient option for treating gout and accompanying arthritis in which the principal problem is joint localized pain. This pain is due to the accumulation of uric acid crystals which leads to joint inflammation. The membrane lining of the joint becomes thick, swollen and the fluid between the joint starts degenerating, which cause friction and severe pain.[4,5] In the suffering patients, there is no choice except analgesics and because of consistent pain, there is continuous use of painkillers which can affect gastrointestinal tract, liver, damage the kidney, and produce most hazardous action of nonsteroidal anti-inflammatory

TABLE 1 Formulation of secondary layer (SL) containing allopurinol (ALP)

Formulation	ALP (mg)	Methocel (mg)	ERL100 (mg)	PEG 400 (%w/w)	Menthol (%)	Clove oil (%)	Methanol (ml)
$KA1_{SL}$	50	50	400	50	—	—	15
$KA2_{SL}$	50	150	300	50	—	—	15
$KA3_{SL}$	50	250	200	50	—	—	15
$KA4_{SL}$	50	350	100	50	—	—	15
$KA1_{SL}$-M_1	50	50	400	50	5	—	15
$KA1_{SL}$-M_2	50	50	400	50	10	—	15
$KA1_{SL}$-M_3	50	50	400	50	15	—	15
$KA1_{SL}$-C_1	50	50	400	50	—	5	15
$KA1_{SL}$-C_2	50	50	400	50	—	10	15
$KA1_{SL}$-C_3	50	50	400	50	—	15	15

drugs (NSAID), that is, ulcer. Although oral analgesics are frequently used for symptomatic care, transdermal administration can be used as an alternate route of therapy. Ketoprofen (KTP), BCS II, is a NSAID which is widely used for the treatment of musculoskeletal pain.[6] Allopurinol (ALP), BCS I, has been used in the clinical management of gout and other condition associated with hyperuricemia as a xanthine oxidase inhibitor.[7] These drugs have ideal physicochemical properties for transdermal patch owing to their appropriate partition coefficient, low molecular weight, high permeability, and half-life.[6] In Asian countries, the transdermal patch has a huge popularity among patients with rheumatoid arthritis and osteoarthritis due to convenience in use, better gastrointestinal profile, and reduction in dosing frequency.[8] Therefore, the aim of this study was to avoid continuous oral medication and to prepare a formulation which produces a specific and effective action without producing side effects. For this purpose, a bilayer matrix transdermal patch was formulated containing KTP as NSAID in primary layer and ALP as antigout in secondary layer. The present research also aimed to evaluate the drug release from transdermal patches by in vitro dissolution studies and to select an optimized formulation for ex vivo permeation studies. The drug release was further enhanced by the use of clove oil and menthol as permeation enhancer (PE) via albino rat's skin.

2 | MATERIALS AND METHOD

2.1 | Materials

Allopurinol (generously gifted by Pharmedic, Pakistan); KTP (generously gifted by Sharooq Pharma, Pakistan); Eudragit L100 (ERL100) (Merck, Germany); Methocel (HPMC E5) (Merck); polyethylene glycol 400 (PEG 400) (Merck); polyvinyl alcohol (Merck); menthol; clove oil (Royal flavor's company, Pakistan); methanol (BDH, England); sodium chloride (Merck); potassium dihydrogen phosphate (Fluka, Germany); disodium hydrogen phosphate (Fluka); sodium hydroxide (Riedel-de Haen); distilled water were used in this study.

2.2 | Method

2.2.1 | Preparation of secondary layer (SL) of ALP

The SL was prepared using the casting solutions of different amounts of polymers (Methocel and ERL 100) with the constant amounts of drug (ALP) and plasticizer (PEG 400) in 15 ml methanol (Table 1) and stirred on the hot plate magnetic stirrer. After complete mixing, the solution was placed in bath sonicator for the removal of air bubbles and sonicated for 30 min. Then, the solution was decanted in a Petri dish containing a backing membrane (casted by pouring 4% w/v polyvinyl alcohol solution followed by drying at room temperature for 24 hr). The secondary layer was allowed to dry by inverted funnel technique at room temperature for 48 hr.[9]

2.2.2 | Preparation of primary layer (PL) of KTP

This layer was formulated using constant amount of drug (KTP), polymer (Methocel), and plasticizer (PEG 400) in 10 ml methanol and stirred well (Table 2). After complete mixing, the casting solution was poured on to the SL and allowed to dry at room temperature for 24 hr by inverted funnel technique.[10] After complete drying, the bilayer patch was peeled off from the Petri dish.

The optimized formulation was selected after in vitro dissolution studies, and PE such as menthol (M)[11] and clove oil (C)[12] was added in it for ex vivo permeation studies.

2.2.3 | Preparation of calibration curve

The calibration curves were constructed by stock solution dilution method. The dilutions of 1, 2, 4, 8, 16, and

TABLE 2 Formulation of primary layer (PL) containing ketoprofen (KTP)

Formulation	KTP (mg)	Methocel (mg)	PEG 400 (%w/w)	Menthol (%)	Clove oil (%)	Methanol (ml)
Without PE	30	50	50	—	—	10
$KA1_{PL}$-M_1	30	50	50	5	—	10
$KA1_{PL}$-M_2	30	50	50	10	—	10
$KA1_{PL}$-M_3	30	50	50	15	—	10
$KA1_{PL}$-C_1	30	50	50	—	5	10
$KA1_{PL}$-C_2	30	50	50	—	10	10
$KA1_{PL}$-C_3	30	50	50	—	15	10

32 μg/ml were prepared. The absorbance of ALP and KTP was estimated at a wavelength of 250 and 258 nm, respectively.[13,14] The curve was obtained by plotting graph between concentration and absorbance, and the slope and regression coefficient (R^2) at 95% confidence interval (CI) were determined by linear equation in MS Excel. The R^2 was 0.999 and 0.997 for ALP and KTP, respectively.

2.2.4 | Evaluation of bilayer transdermal patches

Swelling index of SL of bilayer transdermal patch

The films of area 1 × 1 cm were attached with already weighed coverslips, and weight was noted on digital weighing balance. They were put in large Petri plates having distilled water such that films were entirely dipped in it. The coverslips were taken out after suitable interval of time, blotted, and weighed immediately. The percentage weight increase because of swelling was calculated by the following equation:

$$\text{Swelling index} = (W_2 - W_1)/(W_1)*100$$

where; W_1 is the initial weight and W_2 is the weight after time intervals.

The experiment was discontinued when films began to dissolve in water.[15]

In vitro dissolution studies of PL and SL of bilayer transdermal patch

The in vitro drug release study by dissolution was carried out in USP apparatus II.[16] The test was conducted to evaluate the effect of hydrophobic and hydrophilic polymer and to select optimized formulations for conducting skin permeation study. The dissolution was carried out for a period of 10 hr in 500 ml of PBS (pH 7.4) at a paddle speed of 50 rpm. The dissolution medium was maintained at 37 ± 1°C. A sample of 5 ml was withdrawn after suitable time interval, filtered, and examined by UV-vis spectrophotometer. The absorbance was put in the calibration curve data for the determination of percentage release. The study was carried out in triplicate and average with standard deviation was taken for each formulation using SPSS software.[17]

Ex vivo permeation Studies of PL and SL of bilayer transdermal patch

Ex vivo permeation studies can aid in evaluation of the drug permeation mechanism from a transdermal patch. The study was conducted using Franz diffusion cell (1.4 cm^2, 12 ml volume) at 37 ± 1°C through excised abdominal skin of albino rats. The skin was obtained by method already reported.[2] The samples were withdrawn after suitable interval time, filtered, and examined spectrophotometrically, and percentage drug permeated through rat's skin was estimated with reference to the calibration curve. The study was carried out in triplicate, and average readings with standard deviation were taken for each formulation using SPSS software.[18]

For the analysis of PL and SL layers for release via ex vivo permeation studies, cumulative amount of drug was determined. As ALP was used for sustained drug release, the flux was also estimated for SL. The cumulative amount of drug permeated in μg/cm^2 was plotted against time. Then, the slope obtained by the linear line equation was divided by area of exposed skin surface, that is, 1.4 cm^2 to determine the drug flux (μg/cm^2.hr).

The targeted flux was calculated with following formula:

$$J{\cdot}A = \mathrm{Cl}{\cdot}\mathrm{C_P}{\cdot}W$$

where J: flux in μg cm^{-2} hr; A: area in cm^2; Cl: clearance of ALP (60 ml hr^{-1} kg); C_p: plasma concentration of ALP (0.5 μg/ml); W: average weight of patient.[2]

2.3 | Statistical analysis

The ex vivo permeation studies and flux were statistically evaluated by one-way ANOVA by Tukey's multiple comparison tests at CI of 95% using MiniTab® 17.1.0. Tukey's post hoc pairwise comparisons were performed to compare statistical difference between formulations at different concentration of permeation enhancer, where $p < .05$ was considered as significant.[2]

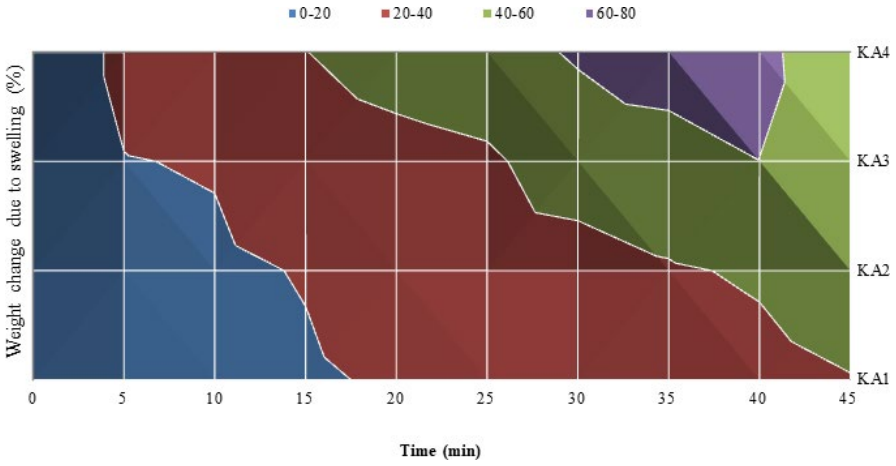

FIGURE 1 Contour plot depicting percentage weight change due to swelling

2.4 | Microscopic analysis

A digital microscope (Optikam B3; Optika Microscope, Italy) was used to analyze the microstructure of matrix patch to ensure the homogeneous dispersion of drug and polymer.[19]

3 | RESULTS AND DISCUSSION

3.1 | Swelling index of SL of bilayer transdermal patch

The percentage weight change was studied by plotting the wire-frame contour graph as shown in Figure 1. The different colors indicated weight change in formulations with respect to time. It is evident from the plot that the weight increase was minimal at lower concentration of Methocel and higher concentration of ERL 100. As the polymer ratio was changed, an increase in weight was observed with respect to time. The zone between $KA3_{SL}$ and $KA4_{SL}$ showed an evident increase in weight after 5 min but started to decrease after 40 min. The result of swelling index signifies that the highest swelling index was obtained in patches with higher concentrations of Methocel. The hydration of polymers, which are frequently used in modified release dosage forms, has been an area of interest as it influences the release of drug from sustained release matrix. The hydrophilic polymers have a high affinity to imbibe water which causes their swelling and makes the system more porous. Thus, it causes a rapid release of drug from the patch which affects its sustained release profile. Furthermore, by adding plasticizer, PEG 400, the density of polymeric network becomes less due to increase in the flexibility and expansion in the free volume between the chains of polymer which makes the polymeric linkage to relax. This leads to an increased penetration of liquid medium into the patch.[20]

3.2 | In vitro drug release of bilayer transdermal patch

The PL (immediate release layer), composed of Methocel, released 100% of drug after 2 hr (data not shown) due to the absence of any rate controlling polymer in the formulation. In the case of SL, the drug release increased with the gradual increase in Methocel concentration due to its hydrophilicity as depicted in Figure 2. Methocel is easily hydrated and a swellable polymer due to which it gives a burst effect and a rapid release as compared to the hydrophobic polymer like ERL 100. The release mechanism from the formulations having Methocel includes imbibition of water into the matrix due to sheer concentration gradient of water at the interface of water and polymer. The water lowers the glass transition temperature of the polymer, and as it becomes equivalent to the system temperature, polymer chain transforms from glassy to rubber-like state. This results in the swelling and volume expansion of the polymer, thereby increasing the dimensions of the system making it porous. The drug starts to dissolve from the matrix when it comes in contact with water, and due to the concentration gradient, it diffuses out of the system.[21,22]

The formulation $KA1_{SL}$ followed zero order ($k_1 = 10.32$ mg/hr) which indicated that the release rate was concentration independent as shown in Table 3. The other formulations followed Higuchi model ($k_3 = 34.30$, 34.19, and 34.43 mg/h$^{0.5}$ for $KA1_{SL}$, $KA1_{SL}$, and $KA1_{SL}$, respectively) which indicated the drug release from the patches through diffusion mechanism.[23] According to Korsmeyer–Peppas (KP)

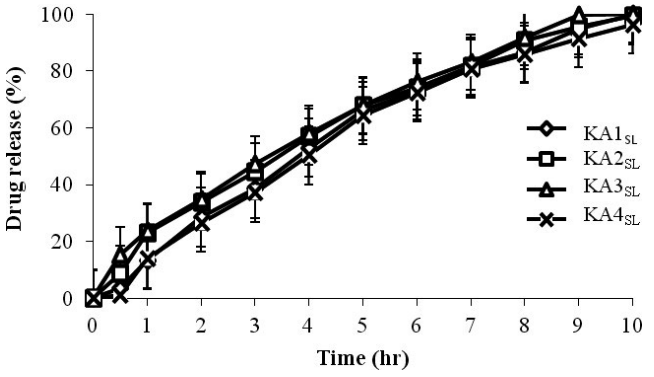

FIGURE 2 In vitro drug release of allopurinol from sustained layer in PBS (pH 7.4)

TABLE 3 Kinetic modeling for in vitro dissolution profile of SL containing ALP (CI of 95%)

	Zero order		First order		Higuchi model		Korsmeyer–Peppas	
Formulation	R^2	k_1 (mg/hr)	R^2	k_2 (hr^{-1})	R^2	k_3 ($mg/h^{0.5}$)	R^2	n (hr^{n-1})
$KA1_{SL}$	.9748	10.32	.7668	0.27	.9672	35.57	.9678	1.03
$KA2_{SL}$	.9658	9.82	.8132	0.20	.9844	34.30	.9791	0.76
$KA3_{SL}$	.9670	9.78	.8876	0.18	.9875	34.19	.998	0.65
$KA4_{SL}$	.9456	9.7	.8678	0.16	.9899	34.43	.993	0.61

ALP, allopurinol.

TABLE 4 Cumulative drug release ($\mu g/cm^2$) from PL containing KTP in control patch and formulations containing permeation enhancers

Time (hr)	0.5	1	2	3	4
$KA1_{PL}$	3,055.83 ± 4.28	6,400.90 ± 23.57	8,739.94 ± 19.29	9,695.67 ± 36.43	11,732.90 ± 12.85
$KA1_{PL}$-M_1	3,835.51 ± 25.72	6,903.92 ± 36.44	9,695.67 ± 30.00	11,657.44 ± 6.43	16,285.21 ± 8.57
$KA1_{PL}$-M_2	5,067.90 ± 17.14	5,570.92 ± 6.43	8,765.09 ± 23.57	11,657.44 ± 48.38	16,939.13 ± 32.14
$KA1_{PL}$-M_3	5,243.96 ± 19.28	5,797.28 ± 34.29	11,028.67 ± 51.44	14,751.01 ± 2.14	17,341.55 ± 6.42
$KA1_{PL}$-C_1	3,810.36 ± 21.43	6,803.32 ± 12.86	9,922.03 ± 4.28	11,858.65 ± 40.71	16,310.36 ± 25.71
$KA1_{PL}$-C_2	5,269.11 ± 15.00	5,797.28 ± 45.00	8,966.29 ± 10.71	11,959.26 ± 49.29	16,788.23 ± 6.43
$KA1_{PL}$-C_3	5,344.56 ± 19.28	6,023.64 ± 25.71	12,789.24 ± 15.00	14,977.36 ± 40.71	17,215.79 ± 10.71

KTP, ketoprofen.

model, the value of n in $KA1_{SL}$ was closer to 1 which according to KP model signifies that the drug release is independent of time and concentration which is the case of zero order. The value of n for $KA2_{SL}$ to $KA4_{SL}$ was between $0.5 < n < 1$ which indicated that the drug release was anomalous, that is, the superposition of Fickian diffusion and erosion.[1]

The one-way ANOVA analysis on in vitro dissolution of ALP indicated that drug release from $KA1_{SL}$ was significantly different from $KA3_{SL}$ and $KA4_{SL}$ ($p < .05$) but was similar to $KA2_{SL}$ ($p > .05$). This signified that increasing the concentration of Methocel from 50 mg to 150 mg does not produce prime increase in drug release from the transdermal patch. Although $KA1_{SL}$ and $KA2_{SL}$ begin to give similar dissolution profiles from 5th hour, the dissolution rate changed at 8th hour where $KA2_{SL}$ released 90% of the drug as compared to 86% drug release from $KA1_{SL}$. The cumulative percentage drug release of $KA1_{SL}$ was 99.65 ± 0.04% in 10 hr with desired sustained release effect (t_{0-8}), as compared to $KA2_{SL}$, so it was selected for ex vivo permeation studies using excised abdominal skin of albino rats.

3.3 | Ex vivo permeation studies of bilayer matrix transdermal patch

For the sake of comparison and to evaluate the effect of PE, ex vivo permeation studies of control patch, without any penetration enhancer, were carried out. The PL and SL of control patch had the least drug release as shown in Tables 4 and 5, respectively. The formulation followed zero-order kinetics with a flux of 512.65 $\mu g\ cm^{-2}$ hr in the SL. The low value of flux for $KA1_{SL}$, as compared to the targeted flux of 1,200 $\mu g\ cm^{-2}$ hr, suggested that it was necessary to add PE in order to increase penetration of ALP through the skin.[22,24]

It was observed that as the methanol concentration was changed from 5% (w/w) to 15% (w/w), concentration of drug release from the film also increased as compared to the control patch. There was a slight increase in cumulative drug release when the amount of menthol was changed from 10% to 15% as given in Tables 4 (PL) and 5 (SL). Thus, indicating that menthol is more effective at lower concentrations. The PL of KA1-M_3 released up to 88% of drug in 4 hr where the SL released 66% of drug after 12 hr as shown in Figures 3 and 4, respectively. The ex vivo drug release of formulations was significantly different ($p < .001$) from each other at different menthol concentrations. The presence of ERL 100 in the SL acted as a retardant and thus affected the release pattern. Terpenes are considered as an ideal candidate due to their relatively low skin irritation.[25] Considering the balance between efficacy and toxicity, terpenes may be favorable penetration enhancers for clinical use.[26] Among terpenes, menthol has been reported to be a better penetration enhancer. It is an alcohol type terpenoid. It was selected for the study because it induces a strong cooling sensation when applied on the skin and anesthetizes the sensation of pain by numbness. This effect may be required to reduce pain due to arthritis and gout. On the basis of this property, it may be advantageous to use it in topical analgesic formulations.[27] Usually, terpenes give their effect of skin permeation by any of these three mechanisms that is, the reversible disruption of highly well-organized lipid domain of stratum corneum; increased diffusivity of drug through stratum

TABLE 5 Cumulative drug release (μg/cm^2) from SL containing ALP in control patch and formulations containing permeation enhancers

Time (hr)	$KA1_{SL}$	$KA1_{SL}$-M_1	$KA1_{SL}$-M_2	$KA1_{SL}$-M_3	$KA1_{SL}$-C_1	$KA1_{SL}$-C_2	$KA1_{SL}$-C_3
0.5	216.39 ± 10.81	1,024.00 ± 60.65	1,305.23 ± 17.88	1,421.03 ± 32.13	1,156.35 ± 10.70	1,255.60 ± 24.96	1,652.63 ± 35.69
1	434.76 ± 39.52	1,751.89 ± 32.11	2,182.01 ± 57.14	2,330.89 ± 53.54	1,884.23 ± 49.96	2,099.29 ± 39.27	2,430.15 ± 14.29
2	732.54 ± 92.90	2,678.29 ± 67.85	4,547.64 ± 89.30	5,325.16 ± 75.00	2,727.92 ± 60.69	4,216.79 ± 10.71	5,209.36 ± 67.83
3	1,844.27 ± 67.90	5,308.62 ± 82.16	5,689.11 ± 3.57	5,854.54 ± 35.72	5,325.16 ± 21.44	5,656.02 ± 67.84	6,317.74 ± 85.71
4	3,154.53 ± 21.43	6,863.65 ± 99.99	7,558.46 ± 14.28	6,450.08 ± 39.81	6,714.77 ± 57.14	7,938.94 ± 78.56	8,584.12 ± 10.71
5	3,432.46 ± 3.57	8,335.97 ± 14.28	8,286.34 ± 57.14	8,749.55 ± 67.85	8,236.72 ± 103.58	8,898.43 ± 96.41	9,791.75 ± 53.56
6	4,623.60 ± 78.54	9,345.09 ± 59.40	9,493.98 ± 107.15	10,288.04 ± 17.85	9,675.95 ± 57.14	10,999.39 ± 14.28	11,495.68 ± 82.13
7	5,278.72 ± 103.57	9,857.92 ± 64.29	10,916.67 ± 92.84	11,545.30 ± 7.14	10,618.90 ± 46.43	12,190.48 ± 29.43	12,289.74 ± 75.00
8	5,616.21 ± 17.85	10,833.95 ± 21.42	12,173.94 ± 60.70	12,819.11 ± 25.00	11,330.25 ± 125.01	12,653.68 ± 67.85	13,067.25 ± 49.99
9	6,172.08 ± 7.14	11,958.87 ± 25.00	13,282.31 ± 49.98	14,192.17 ± 85.71	11,876.16 ± 42.87	13,265.77 ± 71.41	13,679.34 ± 60.74
10	7,045.58 ± 60.70	12,604.05 ± 75.00	14,936.60 ± 7.14	15,416.35 ± 96.46	12,554.42 ± 35.72	14,390.69 ± 92.86	14,771.17 ± 67.88
11	7,621.29 ± 53.57	13,629.71 ± 46.44	16,177.32 ± 64.36	16,706.70 ± 64.28	13,563.54 ± 89.35	15,234.38 ± 75.06	15,416.35 ± 64.27
12	8,137.45 ± 50.01	15,118.57 ± 85.69	17,285.70 ± 17.86	17,583.47 ± 57.13	13,993.66 ± 3.57	16,210.41 ± 39.31	16,756.32 ± 10.72

ALP, allopurinol.

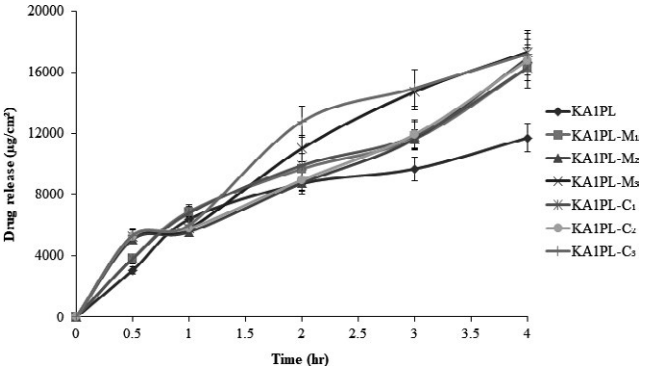

FIGURE 3 Ex vivo cumulative drug release from PL of KTP containing menthol and clove oil as permeation enhancer in PBS (pH 7.4). KTP, ketoprofen

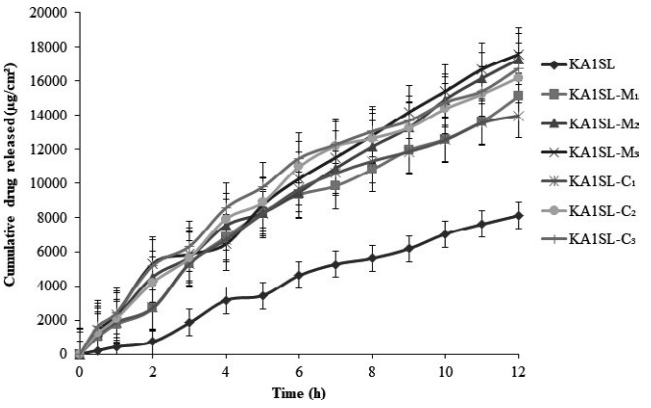

FIGURE 4 Ex vivo cumulative drug release from SL of ALP containing menthol and clove oil as permeation enhancer in PBS (pH 7.4). ALP, allopurinol

corneum by altering intercellular packing[26]; and improved drug partitioning in stratum corneum.[16] The molecular mechanism of menthol is attributed to the preferential hydrogen bonding of oxygen-containing monoterpenes which breaks the transverse hydrogen bonding in lipid bilayer.[26] The concentration of menthol up to 16% has been approved by FDA, and its safety profile has been well established.[24]

An increase in cumulative drug permeation (μg/cm^2) was observed with an increase in clove oil concentration. The PL and SL containing 15% (w/w) of PE showed highest drug release, as depicted in Figures 3 and 4, respectively, but were slightly less than that obtained with 15% (w/w) menthol. The one-way ANOVA denoted that the ex vivo drug permeation through the rat's skin was significantly different ($p < .001$) at varying concentration of clove oil. The essential oil extracted from the dried flower buds of clove, *Eugenia caryophyllata*, is commonly known as clove oil. The clove oil was used in the studies because of its analgesic properties. The drug permeation enhancing effect by clove oil is primarily due to its major component eugenol.[28] The constituents present in essential oils gain entry into the skin lipids and disrupt the well-organized highly ordered domain of stratum corneum lipids.[29]

TABLE 6 Kinetic models of PL of KTP containing permeation enhancers (CI of 95%)

	Zero order		First order		Higuchi model		Korsmeyer–Peppas	
Formulation	R^2	k_1 (μg/hr)	R^2	k_2 (hr^{-1})	R^2	k_3 (μg/$h^{0.5}$)	R^2	n (hr^{n-1})
$KA1_{PL}$-M_1	.9748	15.21	.9088	0.37	.9701	36.38	.9812	0.65
$KA1_{PL}$-M_2	.9695	15.69	.993	0.35	.9387	36.315	.9175	0.57
$KA1_{PL}$-M_3	.9827	17.27	.9473	0.37	.9718	40.99	.9482	0.62
$KA1_{PL}$-C_1	.9784	15.42	.9081	0.37	.9731	36.78	.9859	0.66
$KA1_{PL}$-C_2	.9767	15.34	.9944	0.34	.95	36.29	.9325	0.55
$KA1_{PL}$-C_3	.9454	16.92	.8974	0.36	.972	41.74	.942	0.62

KTP, ketoprofen.

TABLE 7 Kinetic models of SL of ALP containing permeation enhancers (CI of 95%)

	Zero-order kinetics		First-order kinetics		Higuchi model		Korsmeyer–Peppas		Flux
Formulation	R^2	k_1 (μg/hr)	R^2	k_2 (hr^{-1})	R^2	k_3 (μg/$hr^{0.5}$)	R^2	n (hr^{n-1})	(μg cm^{-2} hr)
$KA1_{SL}$-M_1	.9759	3.94	.8114	0.20	.9678	13.0	.9872	0.86	862.62
$KA1_{SL}$-M_2	.9838	4.12	.8396	0.19	.9649	14.62	.9967	0.80	964.43
$KA1_{SL}$-M_3	.9803	4.31	.8434	0.18	.9628	15.12	.9901	0.79	995.15
$KA1_{SL}$-C_1	.9863	4.12	.8102	0.19	.9712	12.76	.9847	0.83	820.15
$KA1_{SL}$-C_2	.9865	4.59	.8005	0.19	.9767	14.39	.9929	0.82	904.33
$KA1_{SL}$-C_3	.9748	4.61	.7969	0.17	.985	14.43	.9900	0.74	921.98

ALP, allopurinol.

The PL of KA1-M_1 ($k_1 = 15.21$ μg/hr), KA1-M_3 ($k_1 = 17.27$ μg/hr), and KA1-C_1 ($k_1 = 15.42$ μg/hr) followed zero-order kinetics, Table 6, which indicates that the drug release from the transdermal patch was independent of the initial drug concentration. The formulation KA1-M_2 ($k_2 = 0.35\ hr^{-1}$) and KA1-C_2 ($k_2 = 0.34\ hr^{-1}$) followed first-order kinetics which signifies that the drug release was dependent on the drug remaining in the transdermal patch. The Higuchi model was followed by KA1-C_3 ($k_3 = 41.74$ μg/$h^{0.5}$) that supports diffusion phenomena. The SL with menthol and clove oil followed zero-order kinetics (Table 7) except for KA1-C_3 that had better fitting in Higuchi model ($k_3 = 41.74$ μg/$h^{0.5}$). The formulations (PL and SL) had anomalous drug release mechanism according to KP model and favored both diffusion and erosion.[23]

An evident increase in flux was seen as the concentration of PE was increased from 5% (w/w) to 15% (w/w) (Table 7). The formulations gave higher flux as compared to the control patch which ensures that PE causes disruption in the stratum corneum and hence aid in the permeation of the drug through the skin. The patch with menthol attained better flux in comparison with those containing clove oil. The highest flux of 995.15 μg cm^{-2} hr was achieved in $KA1_{SL}$-M_3 with 15% menthol concentration. The one-way ANOVA by Tukey's multiple comparison denoted significant difference between the flux rate with $p < .001$ which indicated that flux rate changed with a change in menthol and clove oil concentration.[1]

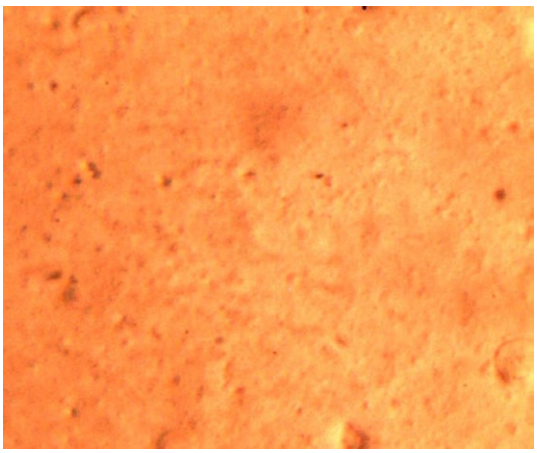

FIGURE 5 Digital microscopy of ALP transdermal layer containing 50 mg drug; ERL 100: Methocel (8:1) and 15% w/w menthol

3.4 | Microscopic analysis of the SL of optimized formulation

The microstructure of the bilayer patch was studied for homogeneous dispersion and network formation of the drug with polymer(s), plasticizer, and PE. The surface morphology of the patch is given in Figure 5. The optic microscopic image ensures the film formation and networked skeleton structure

within the patch that signifies immobilization of PEG 400, menthol, and drug within the polymeric dispersion.

4 | CONCLUSION

Based on the above discussion, it can be concluded that formulation $KA1_{BL}$ (PL: 50 mg Methocel; SL: 50 mg Methocel with 400 mg ERL 100) can be used for transdermal delivery of ketoprofen and allopurinol. Results of the in vitro release study revealed that increasing Methocel concentration in SL increased the drug release through synthetic membrane, whereas ERL 100 acted as a retardant with an increased polymer concentration. The ex vivo release study through the skin revealed higher transdermal flux with higher menthol and clove oil concentration. The results showed that the greatest permeation enhancement was given by $KA1_{SL}$-M_3 containing 15% (w/w) menthol. Thereby, the maximum cumulative drug release with desired flux through skin can be achieved by $KA1_{BL}$-M_3 at 95% CI.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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