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Design and Evaluation of Transdermal Drug Delivery System for Curcumin as an Anti-Inflammatory Drug

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The purpose of this research was to develop a matrix-type transdermal therapeutic system containing herbal drug, curcumin (CUR), with different ratios of hydrophilic (hydroxyl propyl methyl cellulose K4M [HPMC K4M]) and hydrophobic (ethyl cellulose [EC]) polymeric systems by the solvent evaporation technique. Different concentrations of oleic acid (OA) were used to enhance the transdermal permeation of CUR. The physicochemical compatibility of the drug and the polymers was also studied by differential scanning calorimetry (DSC) and infrared (IR) spectroscopy. The results suggested no physicochemical incompatibility between the drug and the polymers. Formulated transdermal films were physically evaluated with regard to drug content, tensile strength, folding endurance, thickness, and weight variation. All prepared formulations indicated good physical stability. In vitro permeation studies of formulations were performed by using Franz diffusion cells. The results followed Higuchi kinetics, and the mechanism of release was diffusion-mediated. Formulation prepared with hydrophilic polymer containing permeation enhancer showed best in vitro skin permeation through rat skin as compared with all other formulations. This formulation demonstrated good anti-inflammatory activity against carrageenan-induced oedema in Wistar albino rats similar to standard formulation.

Keywords curcumin; transdermal film; permeation enhancer; in vitro permeation study

INTRODUCTION

Transdermal drug administration generally refers to topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. For transdermal products, the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin (Misra, 1997).

Transdermal drug delivery has many advantages over the oral route of administration such as improving patient compliance in long-term therapy, bypassing first-pass metabolism, sustaining drug delivery, maintaining a constant and prolonged drug level in plasma, minimizing interpatient and intrapatient variability, and making it possible to interrupt or terminate treatment when necessary (Chien, 1987; Keith, 1983).

Curcumin (CUR), a constituent of *Curcuma longa* (Family *Zingiberaceae*), chemically known as diferuloylmethane, has been reported to possess anti-oxidative (Sreejayan Rao, 1994), anti-inflammatory (Srimol & Dhawan, 1973), anticarcinogenic (Huang, Smart, Wong, & Conney, 1988), and hypocholesterolemic (Rao, Sekhara, Satyanarayana, & Srinivasan, 1970) properties. It is well tolerated in as high a dose as 2 gm/kg (p.o.) in mice (Srimol & Dhawan, 1973). It has been reported to inhibit both lipoxygenase and cyclooxygenase and is a potent scavenger of oxygen-free radicals (Anto, Kuttan, Babu, Rajasekharan, & Kuttan, 1998). Some of the novel formulations developed using CUR include liposomes (Bangham, Hill, & Miller, 1974), solid lipid nanoparticles (Tiyaboonchai, Tungpradit, & Plianbangchang, 2007), transdermal film (Vidyalakshmi, Rashmi, Pramodkumar, & Siddaramaiah, 2004), microspheres (Kumar et al., 2002), nanoemulsion (Wang et al., 2008), and so on. Following oral administration (upto 8 g per day) (Cheng et al., 2001), it is poorly absorbed (Ravindranath & Chandrasekhara, 1980) and only the traces of compound appear in blood. It undergoes extensive first-pass metabolism (Asai & Miyazawa, 2000) and hence is a suitable candidate for transdermal film formulation.

There are reports describing the use of hydroxyl propyl methyl cellulose K4M (HPMC K4M) and ethyl cellulose (EC) transdermal delivery systems as well as other dosage forms for controlled release of drugs (Kusum, Saisivam, Maria, & Deepti, 2003; Limpongsa & Umprayn, 2008; Sakellariou, Rowe, & White, 1986). HPMC K4M is freely water soluble, whereas EC is hydrophobic. So the transdermal delivery systems were prepared using HPMC K4M and EC to study the effect of hydrophilic and hydrophobic nature of polymer on release of CUR.

A large number of fatty acids and their esters have been used as permeation enhancers. Oleic acid (OA) has been shown to be effective as a permeation enhancer for many drugs, for example, increasing the flux of salicylic acid 28-fold and 5-fluorouracil flux 56-fold, through human skin membranes in vitro (Cooper, 1984; Goodman & Barry, 1989). It has also been used for ketoprofen

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(Hu & Zhu, 1996), flurbiprofen (Chi, Park, & Kim, 1995), 5-FU, estradiol (Goodman & Barry, 1988), zalcitabine, didanosine, zidovudine (Kim & Chien, 1996), and so on.

The aims of this study were to (a) develop different matrix films of hydrophilic HPMC K4M and hydrophobic EC polymer with and without permeation enhancer OA containing CUR, (b) perform physicochemical characterization and in vitro permeation studies through rat skin, and (c) compare the anti-inflammatory activity of prepared CUR transdermal films with standard film of diclofenac sodium. The purpose was to provide the delivery of the drug at a controlled rate across intact skin.

MATERIALS AND METHODS

Materials

The following materials were used from the indicated sources without further purification procedures. CUR powder (purity: 65–70%) was received as a gift from Sigma Aldrich (St. Louis, MO, USA). HPMC K4M and EC were generous gift from Colorcon Asia Pvt. Ltd. (Mumbai, India) and Maan Pharmaceuticals Ltd. (Ahmedabad, India), respectively. OA and di-*n*-butyl-phthalate (DBP) were procured from Sigma Chemicals Ltd. (Ahmedabad, India). Other materials used in the study (chloroform, methanol, dichloromethane, glycerol, potassium dihydrogen phosphate, etc.) were of analytical grade. Double-distilled water was used throughout the study.

Methods

Investigation of Physicochemical Compatibility of Drug and Polymer

The physicochemical compatibility between CUR and polymers used in the films was studied by using differential scanning calorimetry (DSC; Shimadzu 60 with TDA trend line software; Shimadzu Co., Kyoto, Japan) and Fourier transform infrared (FTIR-8300; Shimadzu Co., Kyoto, Japan) spectroscopy.

In DSC analysis, the samples were weighed (5 mg), hermetically sealed in flat-bottom aluminum pans, and heated over a temperature range of 50–300°C at a constant increasing rate of 10°C/min in an atmosphere of nitrogen (50 mL/min). The thermograms obtained for CUR, polymers, and physical mixtures of CUR with polymers were compared.

The infrared (IR) spectra were recorded using an FTIR by the KBr pellet method and spectra were recorded in the wavelength region between 4,000 and 400 cm^{-1}. The spectra obtained for CUR, polymers, and physical mixtures of CUR with polymers were compared.

Preparation of Transdermal Films

The matrix-type transdermal films containing CUR were prepared using hydrophilic HPMC and hydrophobic EC polymeric systems (Table 1A). The polymers in different concentrations were dissolved in optimized solvent system containing chloroform:methanol:dichloromethane (4:4:2). DBP (2%, vol/vol) was used as a plasticizer in all formulations. Weighed amount of drug was dispersed in each of the polymeric solutions while stirring to ensure the uniform distribution of drug. The polymeric solution of drug was poured onto the mercury surface (25 cm^2) and dried at room temperature in a dust-free environment. After 24 h, the films were cut into 5-cm^2 pieces and a backing membrane of polypropylene film was glued on. The transdermal films were stored in a desiccator until further use.

To study the effect of OA as a permeation enhancer, different formulations were prepared using the optimized concentration of HPMC (1%, wt/vol) and EC (2%, wt/vol) containing different concentrations of OA (Table 1B).

TABLE 1A
Composition of Film Formulations

	Code					
Materials	H1	H2	H3	E1	E2	E3
CUR	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
HPMC K4M	1% (wt/vol)	2% (wt/vol)	3% (wt/vol)	—	—	—
EC	—	—	—	1% (wt/vol)	2% (wt/vol)	3% (wt/vol)

TABLE 1B
Composition of Film Formulations with Permeation Enhancer

	Code					
Materials	H1O10	H1O20	H1O30	E2O10	E2O20	E2O30
CUR	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
HPMC K4M	1% (wt/vol)	1% (wt/vol)	1% (wt/vol)	—	—	—
EC	—	—	—	2% (wt/vol)	2% (wt/vol)	2% (wt/vol)
OA	10% (vol/vol)	20% (vol/vol)	30% (vol/vol)	10% (vol/vol)	20% (vol/vol)	30% (vol/vol)

Physicochemical Characterization of Films

Thickness. Film thickness was measured using digital micrometer screw gauge (Mitutoyo, Utsunomiya, Japan) at three different places, and the mean value was calculated.

Weight Variation. Weight variation was studied by individually weighing 10 randomly selected films. Such determination was performed for each formulation.

Drug Content. A 5-cm^2 film was cut into small pieces, put into a phosphate buffer (pH 7.2, containing 20%, vol/vol ethanol), and shaken continuously for 24 h. Then the whole solution was ultrasonicated for 15 min. After filtration, the drug was estimated spectrophotometrically at λ_{max} of 425 nm. The preliminary studies indicated that there was no interference of polymers in the absorption wavelengths of the drug.

Flatness. Three longitudinal strips were cut out from each film: one from the center, one from the left side, and one from the right side. The length of each strip was measured and the variation in length because of nonuniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness (Arora & Mukherjee, 2002).

Folding Endurance. Folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking was the folding endurance value.

Percentage of Moisture Content. The films were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 h. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight (Gupta & Mukherjee, 2003).

Percentage of Moisture Uptake. A weighed film kept in a desiccator at room temperature for 24 h was taken out and exposed to 84% relative humidity (a saturated solution of aluminum chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

In Vitro Skin Permeation Studies

In vitro skin permeation studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 21 mL. The excised rat abdominal skin was mounted between the donor and the receptor compartment of the diffusion cell. The formulated films (1 cm^2) were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.2 containing 20% (vol/vol) ethanol to ensure sink condition. Care was taken to remove any bubbles between the underside of the skin and the solution in the receptor compartment. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 37 ± 0.5°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal to maintain sink condition. The cumulative percent amounts of drug permeated per square centimeter of films were plotted against time.

Stability Study

The optimized transdermal films of CUR (H1O20 and E2O30) were subjected to stability study ambient and accelerated (40°C/75% RH) conditions for 365 and 90 days, respectively. The films were packed in aluminum foil and kept at ambient and accelerated conditions. The films were analyzed for drug content and skin permeation kinetics.

Skin Irritation Test

Guidelines of the institutional animal ethics committee were followed for these experiments. The hair on the dorsal side of Wistar albino rats was removed by clipping 1 day before this portion of the experiment (Namdeo & Jain, 2002). The rats were divided into four groups (n = 6). Group I served as the control, group II received transdermal film H1O20 (optimized hydrophilic film), group III received transdermal film E2O30 (optimized hydrophobic film), and group IV received an 0.8% (vol/vol) aqueous solution of formalin as a standard irritant (Mutalik & Udupa, 2004). A new film, or new formalin solution, was applied daily for 7 days. Finally, the application sites were graded according to a visual scoring scale, always by the same investigator.

Anti-Inflammatory Studies

Anti-inflammatory studies of prepared formulations were compared by carrageenan-induced rat paw oedema method in Wistar albino rats. The protocol was approved by the Institutional Animal Ethics Committee. Twenty-four rats were divided into four groups of six rats each for various treatments as shown in Table 1A and B. Group I served as control, groups II and III received formulations H1O20 and E2O30 (containing 2 mg of CUR), respectively, and group IV received diclofenac film (containing 2 mg of diclofenac) as a standard formulation. Subsequently, 30 min after above treatment, 0.1 mL of 1% carrageenan was injected subcutaneously into the planter region of right hind paw to induce oedema (Winter, Risley, & Nuss, 1962). The paw volume was measured initially and at 1, 2, 3, and 4 h after carrageenan injection using plythesmographic method of Harris and Spencer (Harris & Spencer, 1962). Control, test, and standard formulations were applied at the plantar surface of the hind paw with the help of adhesive tape. Same size of film without CUR was applied at the same site with the help of adhesive tape. Percentage inflammation was calculated for comparison.

Statistical Analysis

The data obtained in this study were subjected to statistical analysis using GraphPad-Prism 3.0 Software, for a one-way analysis of variance (ANOVA) following Student–Newman–Keuls multiple comparisons test. p value of less than .05 was considered as evidence of a significant difference.

RESULTS AND DISCUSSION

Investigation of Physicochemical Compatibility of Drug and Polymer

The DSC analysis of pure CUR showed a sharp endothermal peak at 178.02°C, corresponding to the its melting point (Figure 1A and B). The DSC analysis of the physical mixture of the CUR and the polymers revealed a negligible change in the melting point of CUR in the presence of the polymer mixtures studied (173.39°C for the mixture [e] of CUR [a], HPMC [b], DBP [c], OA [d], Figure 1A and 170.23°C for the mixture [g] of CUR [a], EC [f], DBP [c], OA [d] Figure 1B).

The IR spectral analysis of CUR alone showed that the principal peaks were observed at wavenumbers 3,509, 2,366,

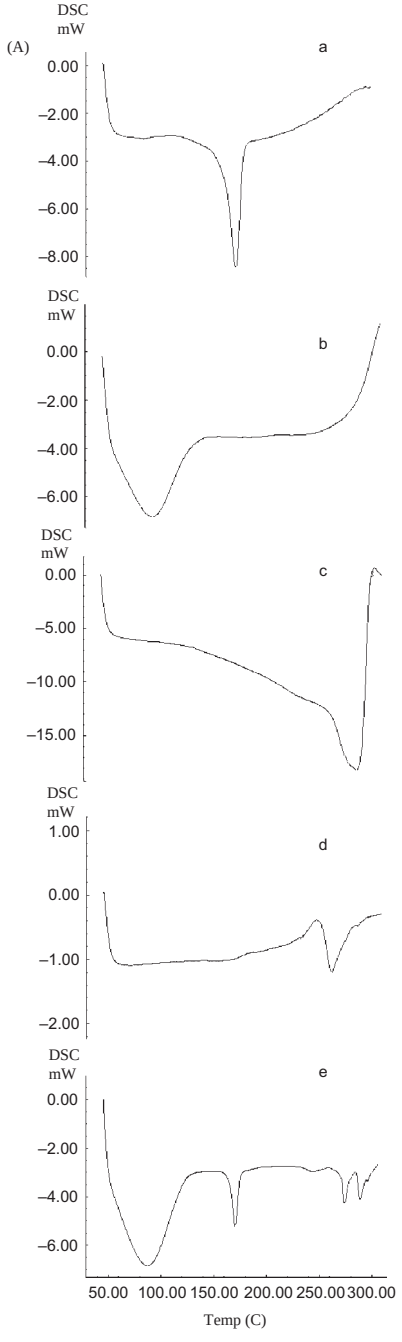

FIGURE 1A. Differential scanning calorimetry (DSC) thermograms of curcumin (a), hydroxyl propyl methyl cellulose (b), di-*n*-butyl-phthalate (c), oleic acid (d), and their physical mixture (e).

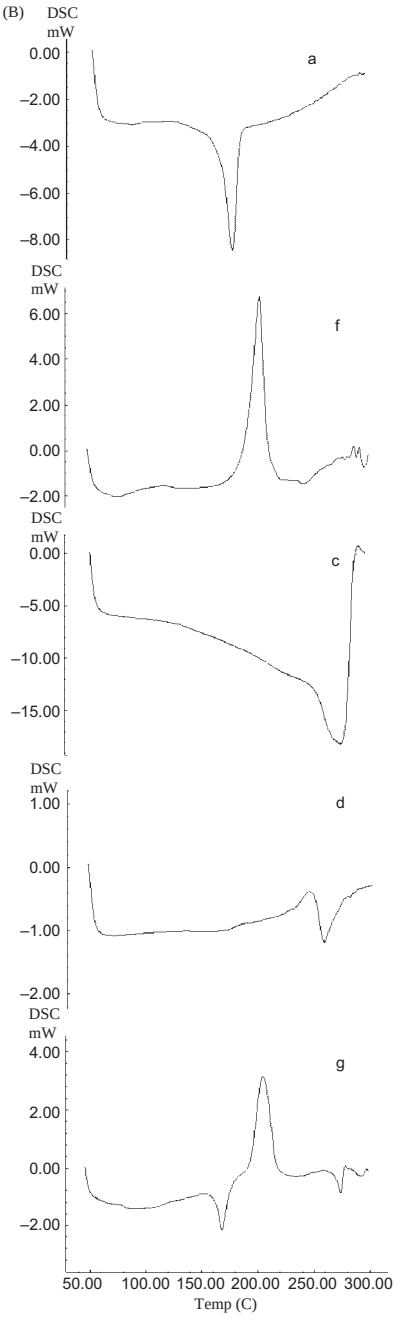

FIGURE 1B. DSC thermograms of curcumin (a), ethyl cellulose (f), di-*n*-butyl-phthalate (c), oleic acid (d), and their physical mixture (g).

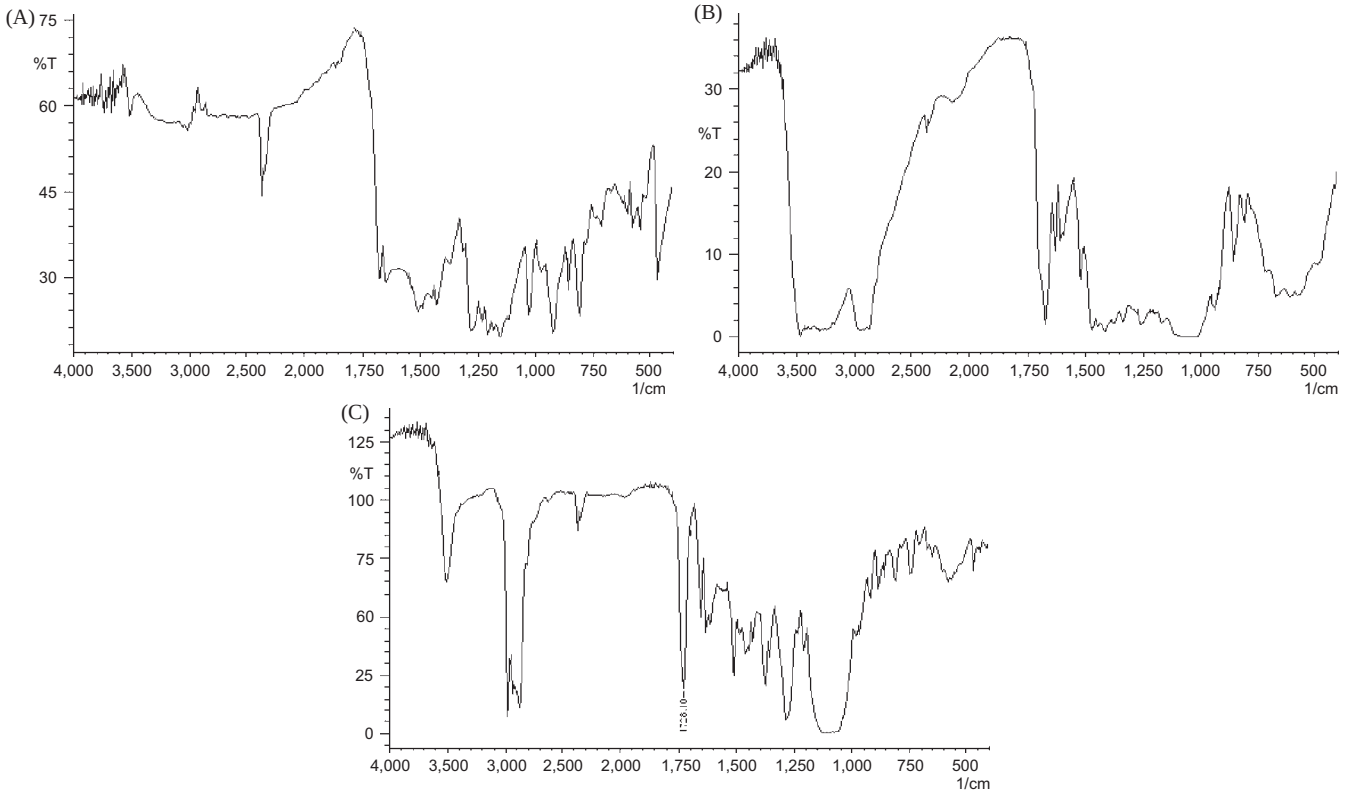

FIGURE 2. Infrared spectra of curcumin (A); physical mixtures of curcumin, hydroxyl propyl methyl cellulose, di-*n*-butyl-phthalate, and oleic acid (B); and curcumin, ethyl cellulose, di-*n*-butyl-phthalate and oleic acid (C).

1,683, 1,512, 1,283, and 927 cm^{-1}, confirming the purity of the drug (Figure 2A). In the IR spectra of the physical mixture of CUR, HPMC, DBP, and OA, the major peaks of CUR were observed at wavenumbers 3,497, 2,370, 1,673, 1,523, 1,270, and 938 cm^{-1} (Figure 2B; for the physical mixture of CUR, EC, DBP, and OA, they were observed at 3,488, 2,372, 1,652, 1,507, 1,289, and 958 cm^{-1} [Figure 2C]). However, some additional peaks were observed with the physical mixture, possibly because of the presence of polymers. The DSC and IR results suggest that the drug and polymers are compatible. Wade and Weller reported that HPMC, EC, polyvinylpyrrolidone (PVP), and other common polymers are popular in controlled and sustained release matrix-type films because of their compatibility with several drugs (Wade & Weller, 1994).

Physicochemical Characterization of Films

The results of the physicochemical characterization of the films are shown in Table 2. The polymeric combinations showed good film-forming properties, and the method of casting on mercury substrate was found to give good films. Low *SD* values were found in the thickness of films, which ensured uniformity of thickness of each film.

The weights ranged between 21.3 and 25.2 mg, which indicate that different batches' film weights were relatively similar. Good uniformity of drug content among the batches was observed with all formulations and ranged from 97.3 to 100.2%. The results indicated that the process employed to prepare films in this study was capable of producing films with uniform drug content and minimal film variability. The flatness study showed that all the formulations had the same strip length before and after their cuts, indicating 100% flatness. Thus, no amount of constriction was observed; all films had a smooth, flat surface; and that smooth surface could be maintained when the film was applied to the skin. Folding endurance test results indicated that the films would not break and would maintain their integrity with general skin folding when applied.

Moisture content and moisture uptake studies indicated that the increase in the concentration of hydrophilic polymer was directly proportional to the increase in moisture content and moisture uptake of the films, whereas increase in the concentration of hydrophobic polymer lead to the decrease in moisture content and moisture uptake of the films. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long-term storage. The moisture uptake of the formulations was also low, which could protect the formulations from microbial contamination and reduce bulkiness (Mutalik & Udupa, 2004).

TABLE 2
Physicochemical Properties of Curcumin Transdermal Films

Code	Thickness (mm)	Weight (mg)	Drug Content (%)	Folding Endurance	% MU	% MC
H1	0.43 ± 0.013	21.3 ± 0.8	99.4 ± 1.5	54 ± 3.4	3.75 ± 2.73	2.77 ± 2.73
H2	0.49 ± 0.016	22.6 ± 1.3	98.4 ± 2.7	51 ± 2.2	4.88 ± 2.84	3.28 ± 2.84
H3	0.54 ± 0.027	23.4 ± 1.4	98.1 ± 3.4	42 ± 3.0	5.91 ± 2.97	3.47 ± 2.97
E1	0.37 ± 0.020	20.2 ± 2.3	98.3 ± 2.8	39 ± 2.1	4.20 ± 2.01	3.70 ± 2.01
E2	0.42 ± 0.026	20.7 ± 1.5	99.8 ± 1.9	47 ± 2.3	3.77 ± 1.76	3.02 ± 1.76
E3	0.44 ± 0.032	22.5 ± 2.2	97.7 ± 2.5	48 ± 3.7	2.21 ± 0.87	2.13 ± 0.87
H1O10	0.45 ± 0.024	22.4 ± 1.7	98.2 ± 3.2	54 ± 2.9	4.21 ± 1.75	3.81 ± 1.75
H1O20	0.47 ± 0.037	23.6 ± 1.1	100.2 ± 2.7	53 ± 3.4	5.72 ± 2.34	4.24 ± 2.34
H1O30	0.50 ± 0.022	24.2 ± 1.4	97.3 ± 2.9	42 ± 2.1	6.55 ± 2.85	5.16 ± 2.85
E2O10	0.42 ± 0.029	23.3 ± 2.3	97.3 ± 2.5	40 ± 2.6	5.27 ± 2.26	3.97 ± 2.26
E2O20	0.44 ± 0.031	24.8 ± 2.4	98.5 ± 3.0	55 ± 3.6	4.63 ± 1.83	3.22 ± 1.83
E2O30	0.45 ± 0.033	24.9 ± 1.6	99.6 ± 1.7	57 ± 3.1	4.08 ± 2.74	2.88 ± 1.74

MU, moisture uptake; MC, moisture content.
All values are expressed as $M \pm SD$ ($n = 5$).

In Vitro Skin Permeation

The in vitro release profile is an important tool that predicts in advance how a drug will behave in vivo (Katayose & Kataoka, 1997). The in vitro skin permeation experiments indicated that release of drug from hydrophilic polymer was more as compared to hydrophobic polymer. Initial rapid dissolution of the hydrophilic polymers occurs when the film is in contact with the hydrated skin, resulting in the accumulation of high amounts of drug on the skin surface and thus leading to the saturation of the skin with drug molecules at all times (Rao & Diwan, 1998). Permeation enhancer increased the release of drug from both hydrophilic as well as hydrophobic polymer.

The cumulative percent amount of drug released from formulations H1 and E2 (84.4 and 48.1%, respectively) was high compared to other formulations prepared without permeation enhancer (i.e., H2, H3, E2, and E3). The cumulative percent amount of drug released from formulations H1O20 and E2O30 (99.8 and 60.5%, respectively) was high compared to other formulations prepared with permeation enhancer (i.e., H1O10, H1O30, E2O10, and E2O20). The order of drug release from all four formulations in decreasing order was H1O20 > H1 > E2O30 > E2. The results of skin permeation studies of CUR from formulations H1, E2, H1O20, and E2O30 are shown in Figure 3.

The in vitro release profiles of H1, E2, H1O20, and E2O30 were subjected to zero-order, first-order, and Higuchi model (Table 3). The in vitro release profiles of the formulations did not fit into zero-order kinetics or first-order kinetics. However, the release profile of the formulated films followed Higuchi's equation, which indicates that the permeation of the drug from the films was governed by a diffusion mechanism. Since many release processes can be represented by a coupling of a Fickian and non-Fickian mechanism, Ritger and Peppas introduced the power law equation $M_t/M_\infty = K_t^n$ to characterize the controlled release behavior of a drug from polymer matrices (Ritger & Peppas, 1987). The value of n can be calculated from the slope

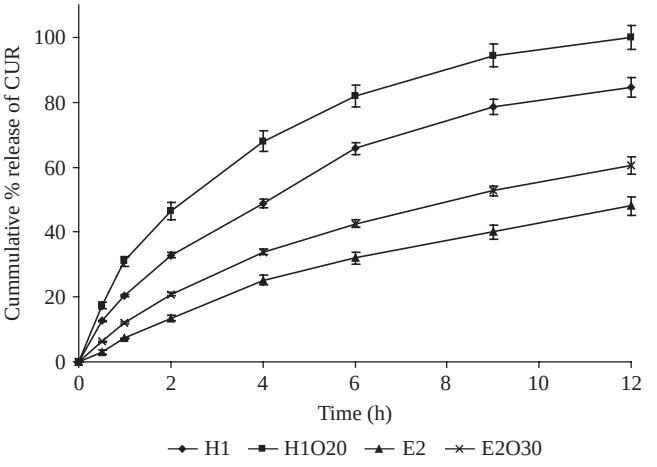

FIGURE 3. In vitro skin permeation studies of curcumin from differentt formulations.

TABLE 3
In Vitro Release Kinetics of Curcumin Through Rat Skin

Batches	Zero Order (r^2 value)	First Order (r^2 value)	Higuchi (r^2 value)	Ritger and Peppas (n value)
H1	0.9332	0.8765	0.9903	0.6137
H1O20	0.8898	0.6068	0.9841	0.5468
E2	0.9609	0.9217	0.9904	0.861
E2O30	0.9507	0.9208	0.9896	0.7107

TABLE 4
Stability Study of Optimized Formulations of Curcumin at Ambient and Accelerated Conditions

Batch	Condition	Parameter	Days 0	7*	15*	30*	90*	180*	270*	365*
H1O20	1	A	101.1 ± 3.8	100.3 ± 4.1	99.7 ± 2.9	98.3 ± 3.7	99.5 ± 4.3	100.2 ± 2.9	99.1 ± 4.4	98.9 ± 3.7
		B	99.3 ± 2.6	99.4 ± 3.1	98.8 ± 3.8	97.3 ± 4.2	97.1 ± 3.1	98.4 ± 3.5	96.3 ± 2.7	97.6 ± 4.0
	2	A	100.6 ± 3.8	99.7 ± 4.0	98.3 ± 3.3	97.3 ± 2.7	96.8 ± 3.7	—	—	—
		B	99.2 ± 2.7	97.3 ± 3.2	96.8 ± 2.9	95.9 ± 2.2	95.2 ± 3.3	—	—	—
E2O30	1	A	99.3 ± 3.3	100.6 ± 4.9	98.3 ± 3.8	100.9 ± 3.6	99.2 ± 4.1	99.5 ± 3.2	98.1 ± 2.8	99.1 ± 3.7
		B	60.7 ± 2.3	59.5 ± 1.9	61.4 ± 2.4	59.3 ± 1.7	60.9 ± 2.1	59.1 ± 2.7	62.8 ± 2.4	60.2 ± 2.0
	2	A	99.1 ± 3.4	98.6 ± 2.6	98.2 ± 3.5	96.8 ± 3.1	95.7 ± 3.6	—	—	—
		B	60.1 ± 2.8	59.6 ± 2.2	58.8 ± 2.9	57.3 ± 2.4	56.4 ± 1.9	—	—	—

Condition 1, ambient condition; 2, accelerated condition (40°C/75% RH) for 90 days. Parameter A, drug content (%); B, cumulative % in vitro release of curcumin at 12 h.

*Analysis of variance (ANOVA) analysis showed that A and B are insignificant ($p > .05$, $n = 6$) at different times compared to 0 day.

of $\ln(M_t/M_\infty)$ versus $\ln(t)$ and can be indicative of the operating release mechanism. The n values obtained by this equation indicated that the amount of drug released by non-Fickian diffusion predominated with all formulations.

Stability Study

The data of stability studies of transdermal films of CUR (H1O20 and E2O30) are summarized in Table 4. The result of this study showed that CUR remained stable in both type of film formulations at ambient and accelerated condition for 365 and 90 days, respectively. No significant ($p > .05$, $n = 6$) variation in drug content and cumulative percent in vitro release of CUR at 12 h was observed at mentioned conditions.

Skin Irritation Test

The skin irritation test of the transdermal formulations H1O20 and E2O30 showed a skin irritation score (erythema and edema) of less than 2 (Table 5). According to Draize, Woodward, and Calvery (1944), compounds producing scores of 2 or less are considered negative (no skin irritation). Hence, the developed transdermal formulations are free of skin irritation.

Anti-Inflammatory Studies

The results of anti-inflammatory activity after topical application of transdermal film are reported in Table 6. Statistical analysis showed that the edema inhibition of H1O20 and standard formulations were significantly different from control group ($p < .05$), whereas E2O30 was not significantly different from control group ($p > .05$). The results also showed that the anti-inflammatory effect of formulation H1O20 was similar to the effect of standard (diclofenac film) ($p < .05$). Hydrophilic film containing permeation enhancer showed better percent inhibition as compared to film prepared using hydrophilic polymer without permeation

TABLE 5
Skin Irritation Scores Following Transdermal Film Application

Rat No.	Control Erythema[a]	Control Edema[b]	H1O20 Erythema	H1O20 Edema	E2O30 Erythema	E2O30 Edema	Formalin Erythema	Formalin Edema
1	0	0	1	0	1	0	3	2
2	0	0	1	1	0	0	3	1
3	0	0	0	0	1	1	2	3
4	0	0	2	1	1	0	3	3
5	0	0	2	2	2	1	3	1
6	0	0	0	1	1	0	3	3
Average			1.00 ± 0.37*	0.83 ± 0.31*	1.00 ± 0.26*	0.33 ± 0.2*	2.83 ± 0.17	2.17 ± 0.40

[a]Erythema scale: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, scar formation.

[b]Edema scale: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, severe.

*Significant compared with formalin ($p < .05$).

TABLE 6
Anti-Inflammatory Activity of Different Transdermal Film Formulations

		Paw Volume (mL)[a] at Time After Carrageenan Injection				
Treatment	No.	Initial	1 h	2 h	3 h	4 h
Control	6	1.58 ± 0.09	2.61 ± 0.20	2.86 ± 0.26	3.01 ± 0.31	3.07 ± 0.33
H1O20[b]	6	1.66 ± 0.14	1.83 ± 0.17 (83.50)	1.95 ± 0.15 (77.34)	1.99 ± 0.19 (76.92)	2.04 ± 0.22 (74.50)
E2O30[c]	6	1.61 ± 0.11	2.11 ± 0.23 (51.46)	2.34 ± 0.28 (42.97)	2.49 ± 0.29 (38.46)	2.56 ± 0.28 (36.24)
Diclofenac film[b]	6	1.60 ± 0.10	1.68 ± 0.13 (92.23)	1.79 ± 0.19 (85.16)	1.87 ± 0.21 (81.12)	1.96 ± 0.24 (75.84)

[a]Values are $M \pm SEM$ (percent reduction).
[b]Analysis of variance (ANOVA) analysis showed that both formulations (H1O20 and diclofenac film) were significantly different from control group ($p < .05$).
[c]Formulation E2O30 was not significantly different from control group ($p > .05$).

enhancer, hydrophobic films prepared with and without permeation enhancer.

CONCLUSION

The drugs of ayurvedic origin can be utilized in a better form with enhanced efficacy by incorporating in modern dosage forms. Transdermal film formulations of CUR, a well-known phytoconstituent, were prepared for improving its anti-inflammatory activity. Transdermal film of CUR prepared with hydrophilic polymer HPMC K4M containing permeation enhancer OA showed best in vitro skin permeation and anti-inflammatory activity as compared to other film formulations. The CUR transdermal films developed in this study have great utility and are a viable option for effective and controlled management of inflammation.

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