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Formulation and evaluation of transdermal patch of Aceclofenac

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Abstract:

The purpose of this research was to develop a matrix-type transdermal therapeutic system containing drug Aceclofenac with different ratios of hydrophilic (hydroxyl propyl cellulose) and hydrophobic (ethyl cellulose) polymeric systems by the solvent evaporation technique by using 15 % w/w of dibutyl phthalate to the polymer weight, incorporated as plasticizer. Different concentrations of oleic acid and isopropyl myristate were used to enhance the transdermal permeation of Aceclofenac. The physicochemical compatibility of the drug and the polymers studied by differential scanning calorimetry and infrared spectroscopy suggested absence of any incompatibility. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, flatness, tensile strength, folding endurance, percentage of moisture content and water vapour transmission rate. All prepared formulations indicated good physical stability. *In-vitro* permeation studies of formulations were performed by using Franz diffusion cells. Formulation prepared with hydrophilic polymer containing permeation enhancer showed best *in-vitro* skin permeation through rat skin (Wistar albino rat) as compared to all other formulations. The results followed the release profile of Aceclofenac followed mixed zero-order and first-order kinetics in different formulation. However, the release profile of the optimized formulation F9 (r^2 = 0.9935 for Higuchi) indicated that the permeation of the drug from the patches was governed by a diffusion mechanism. Formulation F9 showed highest flux among all the formulations and 1.369 fold enhancements in drug permeation. These results indicate that the formulation containing 15 % of oleic acid with 10 % Isopropyl myristate give better penetration of Aceclofenac through rat skin.

Keywords: Aceclofenac, 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 [1]. Transdermal

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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 inter- and intra patient variability, and making it possible to interrupt or terminate treatment when necessary [2,3]

The mode of action of Aceclofenac (ACF) is largely based on the inhibition of prostaglandin synthesis. ACF is a potent inhibitor of the enzyme cyclooxygenase (Cox), which is involved in the production of prostaglandins. *In-vitro* data indicate inhibition of Cox-1 and Cox-2 by ACF in whole blood assays, with selectivity for Cox-2 being evident [4]. ACF has shown stimulatory effects on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit IL-1 activity. *In-vitro* data indicate stimulation by the drug of synthesis of glycosaminoglycan in osteoarthritic cartilage. The duration of morning stiffness and pain intensity are reduced and spinal mobility improved, by ACF in patients with ankylosing spondylitis [5] (Laurent et al., 2000). ACF is metabolized to a major metabolite, 4'-hydroxy ACF and to a number of other metabolites including 5-hydroxy ACF, 4'-hydroxydiclofenac, diclofenac and 5-hydroxydiclofenac [6]

There are reports describing the use of hydroxyl propyl cellulose (HPC) in transdermal patches and ophthalmic preparations [7-9] and ethyl cellulose (EC) transdermal delivery systems as well as other dosage forms for controlled release of drugs [10-12] HPC is freely water soluble, whereas EC is hydrophobic. So the transdermal delivery systems were prepared using HPC and EC to study the effect of hydrophilic and hydrophobic nature of polymer on release of ACF. A large number of fatty acids and their esters have been used as permeation enhancers. Oleic acid 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* [13,14]. It has also been used for ketoprofen [15], flurbiprofen [16], 5-FU, estradiol [14], zalcitabine, didanosine, zidovudine [17], etc.

The aims of the present study were to (1) prepare transdermal patches of ACF using hydrophilic and hydrophobic polymer; (2) optimization of transdermal patch formulation using 3^2 full factorial design; and (3) study the *in-vitro* diffusion behavior of prepared transdermal patch formulations in the presence and absence of penetration enhancer. The purpose was to provide the delivery of the drug at a controlled rate across intact skin.

Materials and Methods

ACF was received as a gift samples from Lincoln Pharmaceticals, Ahmedabad, India. Hydroxyl propyl cellulose (HPC) and ethyl cellulose (EC) were generous gift from Colorcon Asia Pvt. Ltd (Mumbai, India) and Maan Pharmaceuticals Ltd. (Ahmedabad, India), respectively. Oleic acid (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.

Investigation of Physicochemical Compatibility of Drug and Polymer

The physicochemical compatibility between ACF 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 to 300°C at a constant increasing rate of 10°C/min in an atmosphere of nitrogen (50 mL/min). The thermograms obtained for ACF, polymers, and physical mixtures of ACF 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 4000

and 400 cm^{-1}. The spectra obtained for ACF, polymers, and physical mixtures of ACF with polymers were compared.

Preparation of Transdermal Films

Transdermal patches containing ACF were prepared by the solvent evaporation technique in cylindrical glass molds with both sides opens [18]. The backing membrane was cast by pouring a 2 % (*m*/*V*) polyvinyl alcohol (PVA) solution followed by drying at 60 °C for 6 h. The drug reservoir was prepared by dissolving HPC or EC in Chloroform: Methanol (1:1) mixture. Dibutyl phthalate 15 % (*w*/*w* of dry polymer composition) was used as a plasticizer. The drug 50 mg (in 5 mL solvent mixture Chloroform: Methanol) was added into the homogeneous dispersion under slow stirring with a magnetic stirrer. The uniform dispersion was cast on a PVA backing membrane and dried at room temperature. (Table 1) The films were stored between sheets of wax paper in a desiccator.

Table 1: Composition of transdermal patches

Sr. No.	Ingredients	Formulation code					
		A1	A2	A3	A4	A5	A6
1	Drug (mg)	50	50	50	50	50	50
2	HPC	150	200	250	-	-	-
3	EC	-	-	-	150	200	250
4	Dibutyl phthalate* (ml)	0.0215	0.0287	0.0358	0.0215	0.0287	0.0358
5	Methanol (ml)	2.5	2.5	2.5	2.5	2.5	2.5
6	Chloroform (ml)	2.5	2.5	2.5	2.5	2.5	2.5

Note: * 15 % w/w of dibutyl phthalate to the polymer weight, incorporated as plasticizer. The above formula gave patch of 19.63 sq. cm. area

Physicochemical characterization of films

Thickness

The thickness of patches was measured at three different places using a micrometer (Mitutoyo Co., Japan) and mean values were calculated [19].

Weight Variation

The patches were subjected to mass variation by individually weighing randomly selected patches. Such determinations were carried out for each formulation [20].

Table 2: Evaluation of transdermal patches

Parameters	A1	A2	A3	A4	A5	A6
Thickness (µm)	120 ± 3.6	135 ± 4.05	142 ± 4.26	186 ± 5.58	206 ± 6.18	215 ± 6.45
Weight variation (mg cm^{-2})	10.61 ± 0.31	12.51± 0.37	14.97 ± 0.44	10.11 ± 0.30	12.74 ± 0.38	15.13 ± 0.45
Drug content (%)	98.3 ± 2.94	99.0 ± 2.97	98.2 ± 2.94	99.2 ± 2.97	98.7 ± 2.96	97.9 ± 2.93
Folding endurance	209 ± 6.27	213 ± 6.39	210 ± 6.3	234 ± 7.02	245 ± 7.35	238 ± 7.14
Tensile strength (kg cm^{-2})	3.15 ± 0.094	3.51 ± 0.105	3.83 ± 0.114	2.12 ± 0.063	2.25 ± 0.067	2.98 ± 0.089
Moisture content (%)	2.32 ± 0.56	2.92 ± 0.68	4.02 ± 0.89	1.96 ± 0.39	1.78 ± 0.33	1.64 ± 0.31
WVTR (mg cm^{-2} h^{-1})	0.468 ± 0.014	0.482 ± 0.014	0.569 ± 0.017	0.121 ± 0.003	0.268 ± 0.008	0.140 ± 0.004

mean ± SD (n=3)

Table 3: Properties of Transdermal patches containing ACF

F. Code	Thickness (µm)	Weight variation (mg)	Drug content (%)	Folding endurance	Tensile strength (kgcm^{-2})
F1	160 ± 5.60	10.6 ± 10.37	97.9 ± 2.42	198 ± 6.93	2.65 ± 0.092
F2	168 ± 5.88	11.12 ± 0.38	98.6 ± 2.45	202 ± 7.07	2.98 ± 0.104
F3	170 ± 5.95	10.23 ± 0.35	97.5 ± 2.41	215 ± 7.52	3.10 ± 0.108
F4	158 ± 5.53	11.20 ± 0.39	96.9 ± 2.39	218 ± 7.63	2.87 ± 0.100
F5	166 ± 5.81	10.73 ± 0.37	98.8 ± 2.45	220 ± 7.70	2.86 ± 0.105
F6	154 ± 5.39	10.97 ± 0.38	95.8 ± 2.35	200 ± 7.00	2.96 ± 0.103
F7	165 ± 5.77	11.21 ± 0.39	97.8 ± 2.42	208 ± 7.28	3.15 ± 0.110
F8	160 ± 5.61	10.87 ± 0.38	98.6 ± 2.45	196 ± 6.86	3.18 ± 0.111
F9	151 ± 5.28	11.52 ± 0.40	99.9 ± 2.49	212 ± 7.42	3.00 ± 0.106

mean ± SD (n=3)

Drug Content

Patches of specified area (1 cm^2) were dissolved in 5 mL of dichloromethane and the volume was made up to 10 mL with phosphate buffer pH 7.4; dichloromethane was evaporated using a rotary vacuum evaporator at 45 °C. A blank was prepared using a drug-free patch treated similarly. The

solutions were filtered through a 0.45 µm membrane, diluted suitably and absorbance was read at 274 nm in a double beam UV-Vis spectrophotometer.

Flatness

Three longitudinal strips were cut out from each film: 1 from the center, 1 from the left side, and 1 from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness [18].

Folding Endurance

This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance [21].

Tensile strength

In order to determine the elongation as a tensile strength, the polymeric patch was pulled by means of a pulley system; weights were gradually added to the pan to increase the pulling force till the patch was broken. The elongation i.e. the distance traveled by the pointer before break of the patch was noted with the help of magnifying glass on the graph paper, the tensile strength was calculated as kg cm^{-2}.

Percentage of Moisture Content

The films were weighed individually and kept in a desiccators containing activated silica at room temperature for 24 hours. 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 [22].

Water vapour transmission rate (WVTR)

WVTR is defined as the quantity of moisture transmitted through unit area of film in unit time [23]. Glass cells were filled with 2 g of anhydrous calcium chloride and a film of specified area was affixed onto the cell rim. The assembly was accurately weighed and placed in a humidity chamber (80 ± 5% RH) at 27 ± 2 °C for 24 hours.

In-vitro skin permeation studies

In-vitro skin permeation studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 22.5 mL. The excised rat abdominal skin (Wistar albino) was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. 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 32 ± 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 pH 7.4 at each sample withdrawal. The cumulative percentages of drug permeated per square centimeter of patches were plotted against time.

Full factorial design

A 3^2 randomized full factorial design was used in the present study. In this design two factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combination. The amount of Oleic acid (X_1) and the amount of Isopropyl myristate (X_2) were selected as independent variables. The drug release at 8 hrs was selected as dependent variable. The design lay out is depicted in Table 4.

Permeation Data Analysis

The flux (µg cm^{-2} hr^{-1}) of ACF was calculated from the slope of the plot of the cumulative amount of ACF permeated per cm^2 of skin at steady state against the time using linear regression analysis [24,25].

The steady state permeability coefficient (K_p) of the drug through rat epidermis was calculated by using the following equation [26]:

$$Kp = \frac{J}{C} \qquad (1)$$

where J is the flux and C is the concentration of ACF in the patch. The penetration enhancing effect of penetration enhancer was calculated in terms of enhancement ratio (ER), and was calculated by using the following equation [27]:

$$ER = \frac{Kp\ with\ penetration\ enhancer}{Kp\ withought\ penetration\ enhancer} \quad (2)$$

Table 4: 3^2 full factorial design layouts for ACF transdermal patches

Batch No	Variables levels in coded form		Q_{8hr} release (%)	Flux (J) (µg cm^{-2} hr^{-1})	Permeability co efficient (K_P) (cm hr^{-1})	Enhancement ratio (ER)
	X_1	X_2				
F1	-1	-1	70.58	216.54	5.310	1.000
F2	-1	0	84.36	249.97	5.839	1.099
F3	-1	+1	90.31	263.26	6.077	1.144
F4	0	-1	81.13	242.56	6.024	1.134
F5	0	0	91.71	267.23	6.318	1.189
F6	0	+1	93.75	271.66	6.923	1.303
F7	+1	-1	88.14	256.57	6.103	1.149
F8	+1	0	96.90	274.75	6.739	1.268
F9	+1	+1	99.64	279.89	7.274	1.369

Translation of coded levels in actual units

Variables level	Low (-1)	Medium (0)	High (+1)
Amount of Oleic acid (% W/W of drug) X_1	0	5	15
Amount of Isopropyl myristate (% W/W of drug) X_2	0	5	10

Kinetic modeling of drug release

To analyze the mechanism of drug release from the patches, the release data were fitted to the following equations:

Zero-order equation:

$$Q = k_0 t \quad (3)$$

Where Q is the amount of drug released at time t, and k_0 is the release rate.

Table 5: Summary of Results of Regression Analysis for Q_{8hr}

Response	b_o	b_1	b_2	b_{11}	b_{22}	b_{12}
FM	91.35	6.571	7.308	-0.541	-3.732	-2.057
RM	90.99	6.571	7.308	-	-3.732	-2.057

*FM indicates full model and RM indicates reduced model

First-order equation:

$$\ln (100 - Q) = \ln 100 - k_1 t \quad (4)$$

Where Q is the percent of drug release at time t, and k_1 is the release rate constant.

Higuchi's equation:

$$Q = k_2 \sqrt{t} \quad (5)$$

Where Q is the percent of drug release at time t, and k_2 is the diffusion rate constant.

Table 6: Calculation for testing the model in portions

Regression	DF	SS	MS	F	R^2
FM	5	624.96	124.99	105.54	0.9971
RM	4	624.37	156.09	150.83	0.9967
Error					
FM	3	3.55	1.184	-	-
RM	4	4.14	1.035	-	-

*DF indicates: degrees of freedom; SS, sum of squares; F, Fischer's ratio; R^2, regression coefficient; FM, full model; and RM, reduced model.

Stability study of optimized formulation

Stability study was carried out for optimized patch formulation at 40°C temperature in a humidity chamber having 75 % RH for 3 months. After 3 months samples were withdrawn and evaluated for physicochemical properties and *in-vitro* diffusion study.

Results and Discussion

Investigation of Physicochemical Compatibility of Drug and Polymer

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced (i.e. endothermic or

exothermic phase transformations). The thermograms of ACF (A), HPC (B), physical mixture of ACF with excipient of HPC patch formulation (C), EC (D) and physical mixture of ACF with excipient of EC patch formulation (E) are presented in Figure 1. The ACF showed a melting peak at 158.22 °C. Peak of ACF at 158.22 °C was present at the same position i.e. near to 160 ^{o}C in the physical mixture of drug with both HPC and EC patch formulation excipients. This confirmed the physicochemical stability of drug with the formulation excipient used in the study.

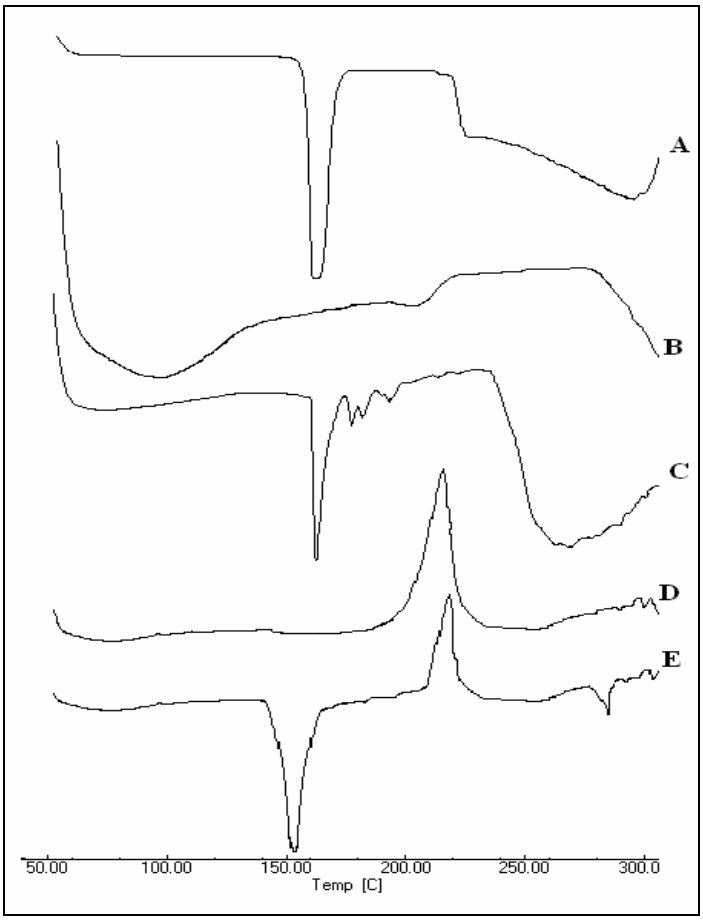

Figure 1: DSC study of ACF (A), HPC (B), physical mixture of HPC formulation excipient with ACF (C), EC (D), physical mixture of EC formulation excipients with ACF (E)

Drug - excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. Infrared (IR) spectra of ACF (A), physical mixture of ACF with excipients of HPC patch formulation (B) and physical mixture of ACF with excipients of EC patch formulation (C) are shown in Figure 2. Infrared absorption spectroscopy (IR) of ACF showed sharp band at 3319, 3278 and 1770 cm^{-1} due to stretching vibration bands of OH, N-H and C=O, respectively. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.

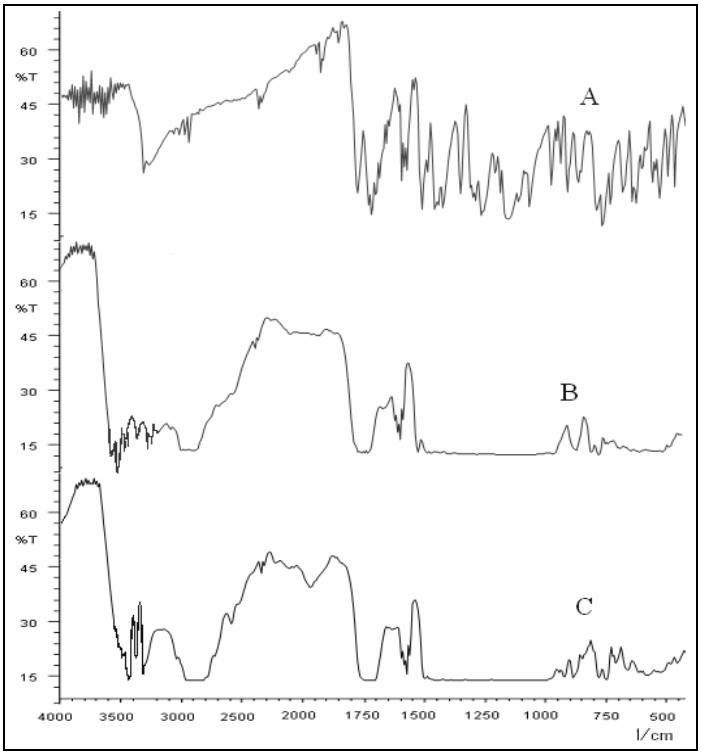

Figure 2: FTIR spectra of ACF (A), physical mixture of HPC with ACF (B), physical mixture of EC with ACF (C)

Table 7: Kinetic modeling of drug release

Formulation code	Zero order	First order	Higuchi
F1	0.9975	0.9966	0.9365
F2	0.9928	0.9925	0.9660
F3	0.9884	0.9901	0.9741
F4	0.9955	0.9951	0.9604
F5	0.9834	0.9838	0.9802
F6	0.9781	0.9809	0.9847
F7	0.9902	0.9885	0.9692
F8	0.9692	0.9669	0.9901
F9	0.9595	0.9576	0.9935

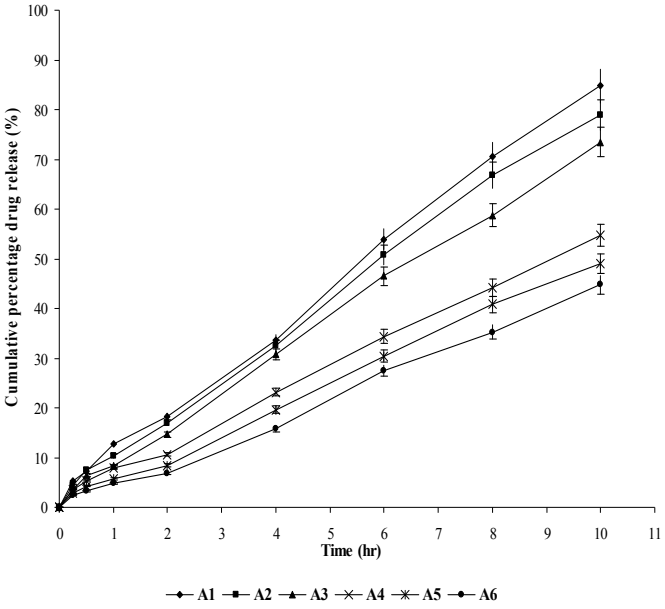

Figure 3: Release profile of ACF from patches containing different concentration of HPC and EC, mean ± SD (n = 3)

Physicochemical characterization of films

The results of the physicochemical characterization of the patches are shown in Table 2. The thickness ranged between 120 ± 3.6 and 215 ± 6.45 μm, which indicate that they are uniform in thickness. The weights ranged between 10.11 ± 0.30 mg and 15.13 ± 0.45 mg, which indicates that different batches patch weights, were relatively similar. Good uniformity of drug content among the batches was observed with all formulations and ranged from 97.9 ± 2.93 % to 99.2 ± 2.97 %. The results indicate that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch 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 patches had a smooth, flat surface; and that smooth surface could be maintained when the patch was applied to the skin. Folding endurance test results indicated that the patches 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 patches. 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 [28].

In-vitro skin permeation

The *in-vitro* release profile is an important tool that predicts in advance how a drug will behave in vivo [29]. The results of *in-vitro* skin permeation studies of ACF from transdermal patches are shown in Figures 3. In the present study hydrophilic (HPC) and hydrophobic (EC) polymers are used to prepared patches. Formulation A1 exhibited greatest 84.8 ± 3.39 % of drug release value, while formulation A6 exhibit lowest 44.73 ± 1.789 % of drug release value. The cumulative amount of drug released from formulations containing hydrophilic polymer release drug at faster rate than hydrophobic polymer. The cumulative amount of drug released from formulations A1, A2 and A3 is much higher than formulation A4, A5 and A6. In addition to nature of

polymer concentration of polymer also affect the drug release. As the concentration of polymer increased

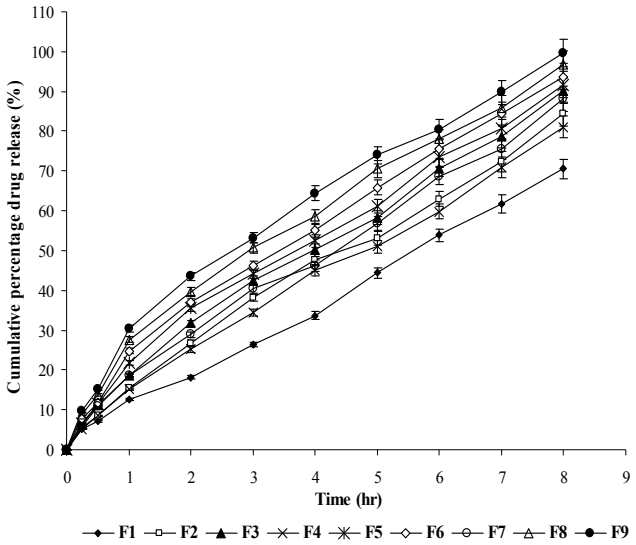

Figure 4: Release profile of ACF from formulation F1 - F9

drug release decreased. The drug release from the patch is ordered as A1 > A2 > A3 > A4 > A5 > A6. Unlike the formulations A2, A3, A4, A5 and A6, the formulations A1 achieved a high cumulative amount of drug permeation at the end of 10 hours. Based on physiochemical and *in-vitro* release experiments, A1 was chosen for further studies.

Full factorial design

Physicochemical properties of factorial design batches

The results of the physicochemical characterization of the patches are shown in Table 3.

In-vitro drug release study of factorial design batches

The cumulative percentage of drug permeated through the rat epidermis from the patch containing different concentration of penetration enhancer is shown in Figure 4. Table 5 shows the results of analysis of variance (ANOVA), which was performed to identify independent factors. The high value of correlation coefficient for Q_{8hr} indicates a good fit. The equation can be used to obtained estimates of the response as a small error of variance was noticed in the replicates. The significant level of coefficients b_{11} was found to be greater than P = 0.05. Hence it was omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 5. The coefficients b_1, b_2, b_{22} and b_{12} were found to be significant at $P < 0.05$. Hence they were retained in the reduced model. An increase in concentration of Oleic acid leads to an increase in Q_{8hr} because the coefficient b_1 bears positive sign. Increasing the concentration of oleic acid from 5 to 10 %, Q_{8hr} value increased from 81.13 % to 88.14 %. An increase in concentration of Isopropyl Myristate leads to increase in Q_{8hr} because the coefficient b_2 bears positive sign. As increasing concentration of Isopropyl myristate from 5 to 10 % the Q_{8hr} value increased from 84.36 % to 90.31 %.

Here the coefficient of interaction terms showed negative value. The interaction term indicate that Q_{8hr} was not significantly affected by interaction of two penetration enhancer. This indicates that by changing two factors at a time there no effect on Q_{8hr}.

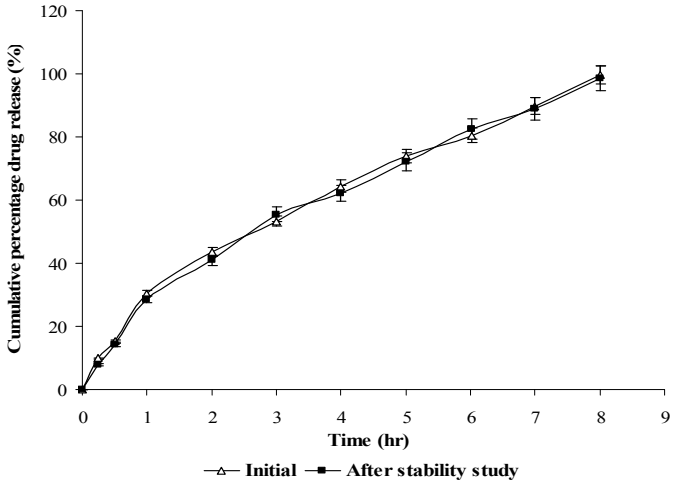

Figure 5: Drug release profile of ACF before and after stability study for formulation F9

The maximum amount (Q_{8hr}) of ACF that permeated during the 8 hr of the study was 99.64 % from formulation F9. The flux was calculated by dividing the cumulative amount of drug permeated per cm^2 of

the skin with time. Thus the corresponding flux of ACF was 216.54 µg cm^{-2} hr^{-1} from formulation F1 (transdermal patch without penetration enhancer). A marked effect of penetration enhancer on ACF permeation was observed when they were incorporated in patch in varying concentration. The cumulative percentage of ACF that permeated over 8 hr was found to increase ranging from 81.13 to 99.64 % for HPC patches. The corresponding flux values were ranging from 242.56 to 256.57 µg cm^{-2} hr^{-1}. Formulation F9 shows highest flux among all the formulation. Formulation F9 shows 1.369 fold enhancements in drug permeation. This result indicate that the formulation containing 15 % of oleic acid with 10 % Isopropyl myristate give better penetration of ACF through rat skin.

Kinetic modeling of drug release

The cumulative amount of drug permeated per square centimeter of patches through rat skin was plotted against time was fitted to zero, first and higuchi kinetic model. As indicated in Table 7, the release profile of ACF followed mixed zero-order and first-order kinetics in different formulation. However, the release profile of the optimized formulation F9 (r^2 = 0.9935 for Higuchi) indicated that the permeation of the drug from the patches was governed by a diffusion mechanism.

Stability study

In order to determine the change in physicochemical parameter and *in-vitro* release profile on storage, stability study was carried out. The physicochemical parameter of the optimized formulation was not significantly changed on storage. The *in-vitro* release profile before and after storage is shown in Figure 5. The result indicates that the formulation was stable on the required storage condition.

Conclusion

The method of preparation of transdermal patches of Aceclofenac presented in this research work is simple. All formulation also showed good physicochemical properties like thickness, weight variation, drug content, flatness, folding endurance, moisture content and moisture uptake. The *in-vitro* release data showed that drug release from the patch formulation have been affected by types of polymer and concentration of polymer. Effect of penetration enhancer like oleic acid and isopropyl myristate have been checked on *in-vitro* permeation of drug. These studies indicated that as the concentration of penetration enhancer increased drug permeation was increased. The finding of this result revealed that the problems of Aceclofenac on oral administration like dissolution rate limited absorption and gastric side effects can be overcome by applying Aceclofenac topically in the form of transdermal patch.

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