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Preparation and *In Vitro* 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 methyl cellulose) and hydrophobic (methyl cellulose) polymeric systems by the solvent casting technique. Formulated transdermal patches 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* drug studies of formulations were performed by using Franz diffusion cells. The results followed the release profile of Aceclofenac followed mixed zero-order. However, the release profile of the optimized formulation F9 (99.50±0.09) 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 217±7.42 fold enhancements in drug permeation.

Keywords: Aceclofenac, Transdermal Patch, *In vitro* drug study.

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INTRODUCTION

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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 simultaneously minimizes the retention and metabolism of the drug in the skin [1]. Transdermal drug delivery has many advantages over the oral route of administration such as improving patient compliance in long term therapy by passing 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]. 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 methyl cellulose (HPC) in transdermal patches and ophthalmic preparations [7-9] and methyl cellulose (EC) transdermal delivery systems as well as other dosage forms for controlled release of drugs [10-12] HPMC is freely water soluble, whereas MC is hydrophobic. So the transdermal delivery systems were prepared using HPMC and MC 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, zalcitabine, didanosine, zidovudine, 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 32 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 [17].

MATERIALS AND METHOD

Hydroxy propyl methyl cellulose was generous gift from Finar Ltd (Gujarat, India) and Methyl cellulose from Research-Lab fine chem. Industries (Mumbai, India). Chloroform from Finar Ltd (Gujarat, India). The patches were prepared by solvent casting method.

Preparation of Transdermal Patches

Weighed quantity of polymer was taken and to this different quantities of solvent was added and vortexes. Sufficient care was taken to prevent the formation of lumps and the boiling tube was set-aside for 1hr to allow the polymer to swell. After swelling, to this mixture, measured quantity of propylene glycol and HPMC was added and vortexed. Finally weighed quantity Aceclofenac was dissolved in remaining quantity of solvent added to the polymer solution and mixed well. It was set aside for 15min to remove any entrapped air and carried out in an oven placed over a horizontal glass surface with temperature being maintained at 40°C. The films were dried for about 12hrs [18].

Table 1: Formulation and Preparation of Transdermal Patches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug(mg)	50	50	50	50	50	50	50	50	50	50
HPMC K15M (mg)	250	500	750	1000	-	-	-	-	-	-
Methyl Cellulose (mg)	-	-	-	-	250	500	750	1000	-	-
HPMCK15M&MC(mg)	-	-	-	-	-	-	-	-	500 500	750 250
Chloroform (ml)	1	1	1	1	1	1	1	1	1	1
Glycerine (ml)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Ethanol (ml)	5	10	15	20	5	10	15	20	20	20

PHYSICO CHEMICAL CHARACTERIZATION OF PATCHES

Physical appearance

All the transdermal films were visually inspected for color, clarity, flexibility and smoothness.

Tensile strength

The films were evaluated using a texture analyzer (Instron Universal Model) equipped with a 500 gm load cell. Film strip in mm X 10 mm of dimension and free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 1 cm. During measurement the film was pulled by top clamp at a rate of 10 mm/minutes [19]. The force and elongation was measured when the films broke. Measurements were run four times for each film. The tensile strength and elongation at break were calculated as below:

Tensile strength (kg/mm2) = Breaking force (kg)/ cross section area of sample (mm2)

Elongation at break %=Increase in length at breaking point (mm)/ Original length (mm) ×100%

Swelling index

Weighed pieces 1×1 cm^2 of film were immersed in distilled water at 0.5, 1, 2, 4, 8 and 24 hrs. Soaked films were removed from the medium at predetermined time, blotted to remove excess liquid and weighed immediately. The swelling index was calculated from the weight increase as follows:

Swelling Index = (W2-W1)/W1

Where W1and W2 are the weight of the film before and after immersion in the medium, respectively.

Weight uniformity

The films of different batches were dried at 60° C for 4hours before testing. Five patches from each batch were accurately weighed in a digital balance. The average weight and the standard deviation values were calculated from the individual weights.

Thickness of the films

The thickness of the drug-loaded polymeric films was measured at five different points using a digital micrometer. The average and standard deviation of five reading were calculated for each film [20].

Folding endurance

The folding endurance was measured manually for the prepared film. A strip of film (2×2 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the films could be folded at the same place without breaking gave the exact value of folding endurance.

Water Vapour Transmission (WVT)

The film was fixed over the glass vial with an adhesive containing saturated solution of potassium chloride 200ml (RH 84%). The cells were taken out and weighed after 1, 2, 3, 4, 5, 6 and 7 days of storage. Water Vapour transmissions were calculated by taking the differences in the weight of the film before and after the study at regular intervals 24 h for at a total period of seven.

Water Vapour Absorption (WVA)

Water Vapour absorption was calculated by taking the difference in the weight of the film before and after the study at regular intervals of 24hrs for a total period of 7 days. For the determination of water Vapour absorption studies of polymer films 3.14 cm^2 areas was taken and weighed accurately and then placed on wire gauge. Which was kept in desiccators containing a saturated solution of potassium bromide (200ml).The humidity was found to be 84% RH. The films were taken out weighed after 1, 2, 3, 4, 5, 6 and 7 days of storage [21].

Percentage Moisture Content

The prepared films were weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24hrs. The films were weighed repeatedly until they showed a constant weight. Values for the percentage of moisture content were calculated using the formula:

Percentage of moisture content = {final weight Initial weight /Initial weight} ×100

Percentage moisture uptake

The weighed films kept in desiccators at room temperature for 24hrs and then exposed to 84% RH using a saturated solution of potassium chloride. The films were weighed repeatedly until showed and a constant weight. A Value for the percentage of moisture uptake was calculated using the formula [22].

Percentage of moisture uptake = {final weight –initial weight/initial weight} × 100

Flatness

Longitudinal strips were cut out each film, one from the center and two from the either side. The length of each strip was measured and variation in the length because of non-uniformity in the flatness was measured by determining percentage constriction, considering 0% constriction is equivalent 100% flatness.

Percentage of constriction=L1-L2/L2×100

Where, L1=Initial length of each strip, L2=Final length of each strip.

Drug content:

Transdermal films of specified area (3.066 cm^2) was cut into small pieces and taken into a 50ml volumetric flask and 25ml of phosphate buffer PH 7.4 was added, gently heated to 45°C for 15 minutes, and kept for 24 hrs with occasional shaking. Then the volume was made up to 50ml with phosphate buffer PH 7.4, similarly, a blank was carried out using a drug-free patch. The solutions were filtered and the absorbance was measured at 273 nm.

***In vitro* drug studies:**

A paddle over disc assembly (USP 23, Apparatus, 2) was used for the assessment of release of drug. The TDDS patch was mounted on the disc and placed at the bottom of the dissolution vessel. The dissolution medium was 900 ml phosphate buffer of PH 7.4. The apparatus was equilibrated to 37±0.5°C and operated at 50rpm. The samples (5ml aliquots) were withdrawn at appropriate time intervals up to 8 hours and analyzed on a UV spectrophotometer at 273nm [23].

RESULTS AND DISCUSSION

The drug loaded patches were formulated using different ratios of plasticizer using the solvent casting technique. All the drug loaded films were thin, smooth, flexible and transparent. As the

concentration of plasticizer increase the physical characters like flexibility, smoothness also improves.

The prepared patches were subjected to thickness, % flatness, tensile, all the loaded films were found to be quite uniform in thickness, % flatness of the drug labelled patches was ideal F9 showed highest tensile strength and the F1 showed lower tensile strength. All the films were uniform in weight.

Drug content analysis of the prepared formulations has shown that the process employed to prepare the patches was capable of giving uniform drug content. Plain HPMC & MC weight uniformity, drug content, moisture content, moisture uptake, swelling index, water vapour transmission, skin irritation and their values are shown in Table No: 2 and 3 patches.

The % swelling index was determined and found too high for F1 and F2. The result from the table clearly indicates the moisture uptake value was found to have direct relationship with swelling index %. As the moisture uptake increases the % swelling index increases. Water vapour transmission values are different in formulation. As the plasticizer concentration increases the thickness, swelling index, water vapour transmission rate, folding endurance also improves.

***In vitro* dissolution of Transdermal patches:**

The % cumulative amount of drug releases from formulations F9 was 99.50%.So it was optimized. When the data was plotted as % cumulative of drug releases vs time and data where depicted on HPMC showed less % cumulative release at initial hours followed.

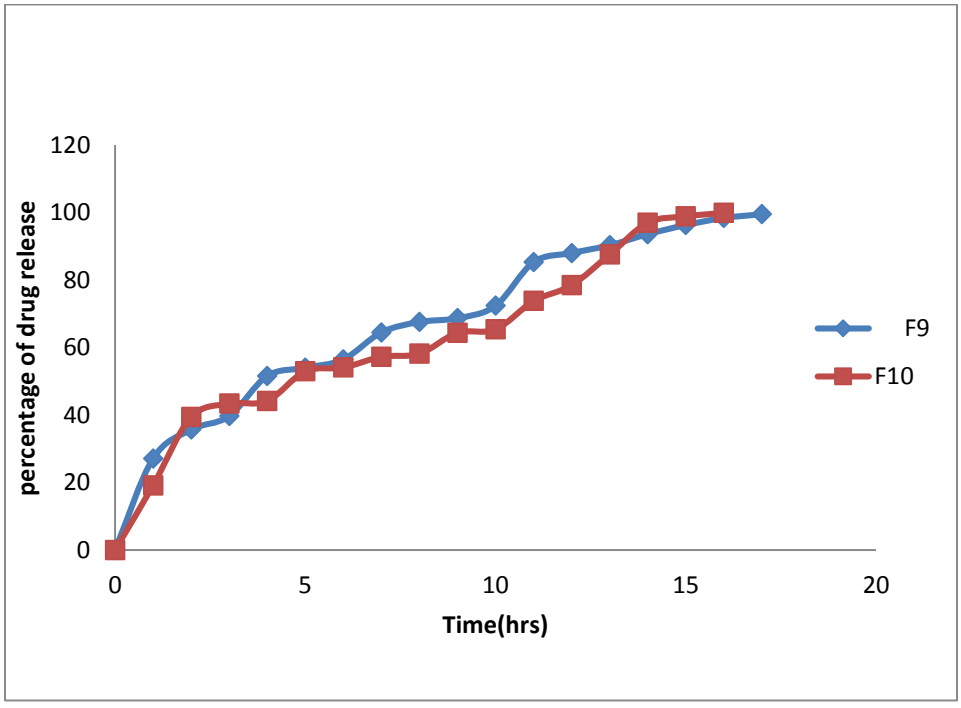

Figure 1: Percentage of Drug Release (Hydroxy Propyl Methyl Cellulose & Methyl Cellulose

Table 2: Physico Chemical Properties of Aceclofenac Transdermal Patch

Formulation Code	Thickness (µm)	Weight Variation (mg)	Drug Content (%)	Folding endurance	Tensile Strength ($kgcm^3$)
F_1	160± 5.60	10.6 ± 10.37	97.9 ± 2.42	198 ± 6.93	2.65 ± 0.092
F_2	168± 5.88	11.12 ± 0.38	98.6 ± 2.45	202 ± 7.07	2.98 ± 0.104
F_3	170± 5.95	10.23 ± 0.35	97.5 ± 2.41	215 ± 7.52	3.10 ± 0.108
F_4	158± 5.53	11.20 ± 0.39	96.9 ± 2.39	218 ± 7.63	2.87 ± 0.100
F_5	166± 5.81	10.73 ± 0.37	98.8 ± 2.45	220 ± 7.70	2.86 ± 0.105
F_6	154± 5.39	10.97 ± 0.38	95.8 ± 2.35	200 ± 7.00	2.96 ± 0.103
F_7	165± 5.77	11.21 ± 0.39	97.7 ± 2.42	208 ± 7.28	3.15 ± 0.110
F_8	160± 5.61	10.87 ± 0.38	98.6 ± 2.45	196 ± 6.86	3.18 ± 0.111
F_9	151± 5.28	11.52 ± 0.40	99.9 ± 2.49	217± 7.42	3.00 ± 0.106
F_{10}	152 ± 5.43	11.71 ± 0.42	99.5 ± 2.46	215 ± 7.18	2.80± 0.107

Table 3: Physico Chemical Properties of Transdermal patch of Aceclofenac

Formulation Code	Moisture content (%)	Moisture uptake (%)	Water vapour transmission (gm/cm. Day)	%swelling index 5 min	10 min	30 min	60 min
F1	5.7	11.5	8.55×10^{-3}	3.2	75.7	76.8	78.6
F2	6.6	12.8	16.00×10^{-3}	75.5	77.1	78.5	79.0
F3	16	17.5	18.2×10^{-3}	66.3	67.5	70.1	72.2
F4	15.7	19.2	20.1×10^{-3}	67.0	68.2	72.3	78.3
F5	16.2	15.5	12.0×10^{-3}	70.4	73.4	74.1	75.5
F6	14.6	14.3	13.88×10^{-3}	62.1	64.3	66.0	67.7
F7	14.3	12.5	13.88×10^{-3}	71.34	72.4	74.1	76.8
F8	16.8	14.8	13.88×10^{-3}	68.2	67.1	69.1	68.1
F9	11.2	13.5	12.88×10^{-3}	60.4	63.4	64.1	65.1
F10	12.5	13.2	13.88×10^{-3}	65.4	66.3	67.1	65.1

CONCLUSION

Transdermal drug delivery systems are ideally suited for drugs that undergoes hepatic first pass metabolism along with a short elimination half-life of less than 3 hours. Aceclofenac transdermal patch prepared by using combination of HPMC & MC. Among all the formulationsF9 showed optimum sustained release characteristics. Hence it can concluded the HPMC&MC (50:50) with 30% plasticizer may be suitable for development of transdermal drug delivery systems of Aceclofenac.

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