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Development and evaluation of transdermal patches of aceclofenac

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Abstract

The aim of this study was to develop and evaluate matrix-type transdermal therapeutic system containing aceclofenac with different ratios of hydrophilic polymers (hydroxylpropyl methylcellulose, sodium carboxy methylcellulose) and a hydrophobic polymer (ethyl cellulose).Thirteen aceclofenac transdermal patch formulations consisting of hydroxyl propyl methyl cellulose, ethyl cellulose and sodium carboxy methyl cellulose polymeric combinations were prepared by solvent casting. These prepared transdermal patches were evaluated for *in vitro* release, weight variation, moisture content, folding endurance, thickness, drug content and swelling studies. The diffusion studies were performed by using modified Franz diffusion cell. The formulation, F10 showed the maximum release of 98.18 % in 4 h, where as F2 showed the maximum release of 93.22 % in 8 h. Formulation, F9 showed the minimum release of 41.4 % in 8 h. Hence F2 (ethylcellulose: hydroxylpropyl methylcellulose ratio 3:2), exhibited good physicochemical properties, zero order *in-vitro* drug release and flux was selected as the best among all for transdermal drug delivery. So it can be reasonably concluded that aceclofenac can be formulated into the transdermal matrix type patches to sustain its release characteristics.

Key Words: Aceclofenac, Transdermal drug delivery, HPMC, Ethyl cellulose, *In-vitro* release

Introduction

Transdermal drug delivery has selectively achieved convenient and painless method of drug delivery, improving patient compliance, reducing adverse effects, and maintaining more consistent and prolonged blood levels. The technology was quickly accepted by patients and clinicians alike, and patches were viewed as a desirable platform for a variety of therapeutic uses, including motion sickness, hypertension, and angina, hormone therapy, smoking cessation, and pain control [1]. Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. The transdermal routes of drug delivery is gaining acceptance and accolades with the demonstration of percutaneous absorption of a large number of drugs and prodrugs and TDDS have been

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developed with objective of systemic medication through application. Judicious choice of drug substance is the most important decision in the successful development of transdermal product. The drug with low effective concentration, short biological half life, wide therapeutic index, having extensive presystemic metabolism, free from skin irritation, low molecular weight, lipid-water penetration coefficient of 2 or greater, etc is a good candidates.

Rheumatoid arthritis (RA) forms a major prototype of rheumatic diseases and is a common cause of disability. Currently synthetic drugs form a major line of treatment in the management of arthritis. The conventional drug treatment of RA consists of analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) [2]. Aceclofenac is a Non-steroidal anti-inflammatory drug (NSAID) used for relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. It is a phenyl acetic acid derivative and an inhibitor of prostaglandin synthesis. This drug is readily absorbed from the gastrointestinal tract, peak plasma concentration occur about 4 h after a dose, 99 % of dose is bound to plasma protein. Unfortunately, the systemic administration of this drug, similar to other NSAIDs, presents gastrointestinal side effects that could be avoided by using a topical application [3]. The oral administration of aceclofenac causes, nausea, vomiting, GI ulcers and GI bleeding with chronic use. Because of GI bleeding, it also causes anaemia. The transdermal route eliminates these side effects, avoids first pass metabolism, increases patient compliance, and maintains the plasma drug level for a longer period of time. Aceclofenac is a highly lipophilic drug and its physiochemical properties suggest that it has good potential for transdermal drug delivery [4].

Polyvinylpyrollidone and ethylcellulose were used to prepare matrix type transdermal patches of aceclofenac [5]. A fixed 10 % w/w amount of dibutylphthalate was used as plasticizer in prepared formulations. Prepared formulations were effective in controlling the release of drug for 10 h or more. Effect of penetration enhancer like oleic acid has been checked on *in-vitro* permeation of drug and was found to be effective. Drug release obeyed first order kinetics in all formulations. Gelatin, polysodium carboxymethylcellulose (CMC) and polyvinylalcohol were used to prepare mucoadhesive patch of aceclofenac [6]. The optimized batch formulation containing gelatin 4.5 %, poly sodium CMC 5.5 %, and propylene glycol 5 % was the best formulation. The folding endurance, mucoadhesive time, drug release (after 8 h) were 325, 268 min, 88.4% respectively, for the optimized formulation. Transdermal patches had also been developed for local action of aceclofenac using Eudragit L100, L100-55 and S100 [7]. The effect of different plasticizers, like propylene glycol and polyethylene glycol (PEG 400) was investigated on the in vitro drug release. The patch prepared with Eudragit L100 had an acceptable percentage drug release after 60 min and the increase of plasticizer concentrations increased drug release.

In the present investigation aceclofenac is chosen as a model drug to explore its potential in being delivered through intact skin. This drug is being extensively used for the treatment of arthritis in conventional dosage forms. Ethylcellulose is a nontoxic, nonallergic, and nonirritating material which possesses good film forming properties with the limitation of poor water permeability. The benefits of ethycellulose may be utilized by mixing with other hydrophilic polymers. In the present study, we developed a suitable matrix film for aceclofenac by employing ethylcellulose, hydroxypropyl methylcellulose, and sodium carboxy methylcellulose (Na-CMC) and to study the effect of polymers on the physicochemical properties of transdermal film and in vitro drug release and permeation studies.

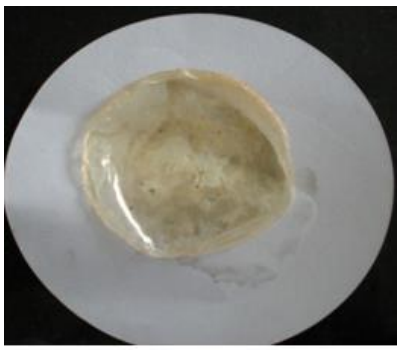

Figure 1 Aceclofenac transdermal patch prepared by solvent casting

Materials and Methods

Materials. Aceclofenac was procured from Yarrow Chem Products, Mumbai, India. HPMC, ethylcellulose, poly ethylene glycol 400, Tween 80, and glyceryl tristearate were purchased from Central Drug House, Delhi. Na-CMC was purchased from Lobachemie, Mumbai, India. All other chemicals and reagents used were of analytical grade and purchased from Rankem, New Delhi.

Preparation of Transdermal Patches of Aceclofenac. Transdermal patches containing aceclofenac were prepared by solvent casting technique. The polymers were dissolved by mixing them in suitable solvents (e.g., ethanol, or water). Aceclofenac was added to the polymer-solvent mixture and stirred well until a homogeneous solution was obtained. The prepared solution was poured in a petridish. The rate of evaporation was controlled by placing the funnel over the petridish. After drying at room temperature for 24 h, membrane was taken out, cut, packed in aluminium foil and stored in desiccator until further use.

Evaluation of transdermal patches of aceclofenac. The prepared patches were evaluated for weight uniformity, thickness, folding endurance, swelling index, moisture content, drug content, in-vitro release study.

Folding Endurance.The endurance power of the drug was determined by repeatedly folding a small strip of films at the same place till it broke. The number of times, the

films could be folded at the same place without breaking gave the value of folding endurance [8, 9].

Weight variation. For weight variation test, each film were weighed individually and the average weight and standard deviation were calculated [10, 11].

Thickness. Thickness of the films was measured at six different points using a screw gauge and average thickness of three films was measured [12, 13].

Moisture content. The patches were weighed and kept in a dessicator containing calcium chloride at 40º C for 24 h. The final weight was noted when there was no further change in the weight of patch. The percentage of moisture content was calculated as difference between initial and final weights with respect to initial weight [14, 15].

$$\text{Moisture Loss (\%)} = \frac{(\text{Initial weight} - \text{Final weight}) \times 100}{\text{Initial weight}} \quad [1]$$

Swelling study. The drug loaded patch of size 1×1 cm^2 was weighed on a pre-weighed cover slip. It was kept on a petridish and 50 ml of phosphate buffer (pH7.4) solution was added. After 30 min the cover slip was removed wiped with tissue paper and weighed. The difference in the weight gave the increase in weight due to the absorption of water and swelling of patch. The degree of swelling, in percent, (S) was calculated using the formula:

$$S\ (\%) = \frac{(W_t - W_o) \times 100}{W_o} \quad [2]$$

Where, W_t is the weight of swollen patch at time t and W_o is the weight of original patch at time zero [16-18].

Drug content. The uniformity of drug content of the transdermal patch was determined, based on dry weight of drug and polymer used, by means of a UV/VIS spectrophotometer method. The formulated patch was cut into pieces and dissolved in 10 ml of methanol. The resulting solution was transferred to a volumetric flask, appropriate dilutions were made with phosphate buffer pH 7.4, filtered through 0.22 μm filter, and analyzed for aceclofenac content at 271.1 nm by a UV-visible spectrophotometer [16, 19].

In vitro drug release study. In vitro release study was carried out in a two compartment apparatus consisting of an open end cylinder (donor compartment) in a glass beaker (receptor compartment) kept over a magnetic stirre. Commercial dialysis membrane-150, Himedia was employed in this study. The membrane used was transparent and regenerated cellulose type, which was permeable to low molecular weight substances. A film of area 3.79 cm^2 was cut tied to one end of an open ended cylinder, which acted as donor compartment. The entire surface of the membrane was in contact with the receptor compartment containing 300 mL of phosphate buffer [pH 7.4] maintained at 37±1 °C. The content of the compartment was agitated by a magnetic stirrer. Samples of 1 ml were withdrawn from receptor compartment and replaced by equal volumes of fresh media. The withdrawn samples were analyzed using UV-visible spectrophotometer at 271.1 nm using reagent blank [20, 21].

Table 1 Compositions of various aceclofenac transdemal patches

Formulation Code	Aceclofenac (mg)	Ethyl cellulose (mg)	HPMC (mg)	Sodium CMC (mg)	Glyceryl triacetate (ml)	Tween 80 (ml)	PEG-400 (ml)
F1	500	300	100	-	-	1	1
F2	500	300	200	-	-	1	1
F3	500	300	300	-	-	1	1
F4	500	400	100	-	-	1	1
F5	500	400	200	-	-	1	1
F6	500	400	300	-	-	1	1
F7	500	500	100	-	-	1	1
F8	500	500	200	-	1	1	-
F9	500	500	300	-	1	1	-
F10	500	-	500	-	1	1	-
F11	500	500	-	-	1	1	-
F12	500	-	100	500	1	1	-
F13	500	-	200	400	1	1	-

Mathematical modeling of release kinetics. The *in vitro* drug release data were fitted to various release kinetic models (14), *viz.* zero-order kinetic model $M_o - M_t = k_o t$, first-order model $\ln (M_t/M_o) = k_1 t$, Higuchi model $M_t = K t^{1/2}$, and Hixon-Crowell cube root model $(W_o)^{1/3} - (W_t)^{1/3} = k_{1/3} t$, where M_o, M_t and M_{∞} correspond to the drug amount taken at zero time, dissolved at a particular time (t) and at infinite (∞) time, respectively. The terms of W_o and W_t refer to the mass of the drug taken initially and at time t, respectively. Various other terms, *viz.* k_o, k_1, K and $k_{1/3}$ refer to the release kinetic constants obtained from the linear curves of zero-order, first-order, Higuchi model and Hixson-Crowell cube root law, respectively.

Results and Discussion

Thirteen different transdermal patches of aceclofenac were prepared by solvent casting technique with polymers like HPMC, Na-CMC, and ethyl cellulose. The compositions of various transdermal patch formulations are presented in Table 1. Prepared patches were cut into circular pieces of 2.2 cm diameter and subjected to various evaluation tests.

Evaluation of aceclofenac transdermal patches. The physical characteristics of various patches are given in Table 2. Folding endurance test results indicated that the patches would not break and would maintain their strength and integrity with the skin folding when used. Most folding endurances of the patches containing glyceryl triacetate (F8-F13) were higher as compared to those containing PEG-400 (F1-F6), as plasticizers, except F7, which showed a good folding endurance.

The weight variations of different patches ranged between 78.00 ± 1.00 mg to 129.66 ± 3.21 mg which were relatively similar. The thicknesses of the patches varied from 0.119 ± 0.002 mm to 0.188 ± 0.001 mm with low standard deviation values in the film thickness measurements ensured uniformity of patches. The weights of different patches of individual batches were very similar to each other. The weights of formulation containing maximum concentration of HPMC were higher as compared to others. It may be due to higher moisture uptake property of HPMC.

The thicknesses of all transdermal patches ranged 0.119 mm to 0.188 mm. This variation in thickness could be attributed to the concentrations of polymers, *i.e.* increase in polymer concentration resulted in increase in the patch thickness. The moisture loss ranged 1.06 ± 0.00 % to 7.23 ± 0.45 %. The moisture content varied to a small extent in all formulations. There was an increase in the moisture content with an increase in hydrophilic polymer (HPMC) concentration in matrix transdermal patches F3, F6, F9, or F10 in the Table 2). Small moisture remains in formulation could help the film to remain stable and free from complete drying. The swelling of patches was observed in phosphate buffer solution (pH 7.4) and an increase in weight was observed due to the swelling, which was at the maximum for F9 containing combination of HPMC and EC and followed by F13 containing Na-CMC and HPMC. F11 exhibited the least swelling due to the only presence of EC (a hydrophobic polymer). The series of F1 to F3, F4 to F6, F7 to F9 containing 300, 400, 500 mg of EC, respectively with increasing concentrations of HPMC exhibited an increase in swelling with an increase in HPMC concentration. Hence it can be the concluded that the concentration of hydrophilic polymer HPMC played a major role in causing swelling.

The results of drug content of all prepared patches indicated that the drug was uniformly dispersed. The drug content ranged from 94.37 % to 98.85 %.

Table 2 Results of physical evaluation tests conducted on aceclofenac transdermal patches (average ± SD, n = 3)

Formulation Code	Weight (mg)	Thickness (mm)	Folding Endurance	Swelling Index (%)	Moisture content (%)	Drug content (%)
F1	80.33 ± 1.5	0.121 ± 0.001	190.66 ± 0.57	36.25 ± 1.25	1.66 ± 0.72	94.37 ± 1.52
F2	94.00 ± 2.0	0.127 ± 0.003	212.33 ± 2.08	51.76 ± 0.61	1.06 ± 0.00	95.71 ± 0.38
F3	109.00 ± 5.0	0.151 ± 0.001	242.00 ± 5.56	74.30 ± 0.91	3.05 ± 0.5	97.75 ± 0.70
F4	90.00 ± 1.00	0.128 ± 0.001	217.00 ± 1.00	41.85 ± 0.64	2.59 ± 0.641	98.57 ± 0.43
F5	105.66 ± 3.21	0.163 ± 0.001	243.66 ± 5.68	54.60 ± 1.98	2.85 ± 0.00	98.75 ± 0.30
F6	118.66 ± 1.15	0.170 ± 0.002	272.00 ± 6.00	81.35 ± 0.85	5.08 ± 0.85	98.71 ± 1.37
F7	108.00 ± 1.00	0.158 ± 0.001	247.33 ± 3.05	37.34 ± 0.53	2.15 ± 0.53	97.09 ± 2.16
F8	116.66 ± 1.15	0.175 ± 0.002	274.00 ± 3.60	62.35 ± 0.50	4.02 ± 0.50	96.94 ± 0.72
F9	129.66 ± 3.21	0.188 ± 0.001	296.33 ± 4.50	98.70 ± 0.45	7.23 ± 0.45	98.85 ± 0.93
F10	83.33 ± 1.52	0.119 ± 0.002	245.00 ± 5.56	92.76 ± 1.20	6.46 ± 1.43	98.51 ± 0.29
F11	78.00 ± 1.00	0.123 ± 0.003	262.33 ± 4.50	28.20 ± 1.28	1.25 ± 0.05	95.95 ± 0.65
F12	110.33 ± 3.51	0.157 ± 0.002	264.33 ± 15.56	86.66 ± 0.52	3.93 ± 0.52	97.13 ± 1.36
F13	113.66 ± 1.15	0.165 ± 0.002	254.66 ± 2.51	92.91 ± 2.34	3.23 ± 0.50	97.37 ± 1.15

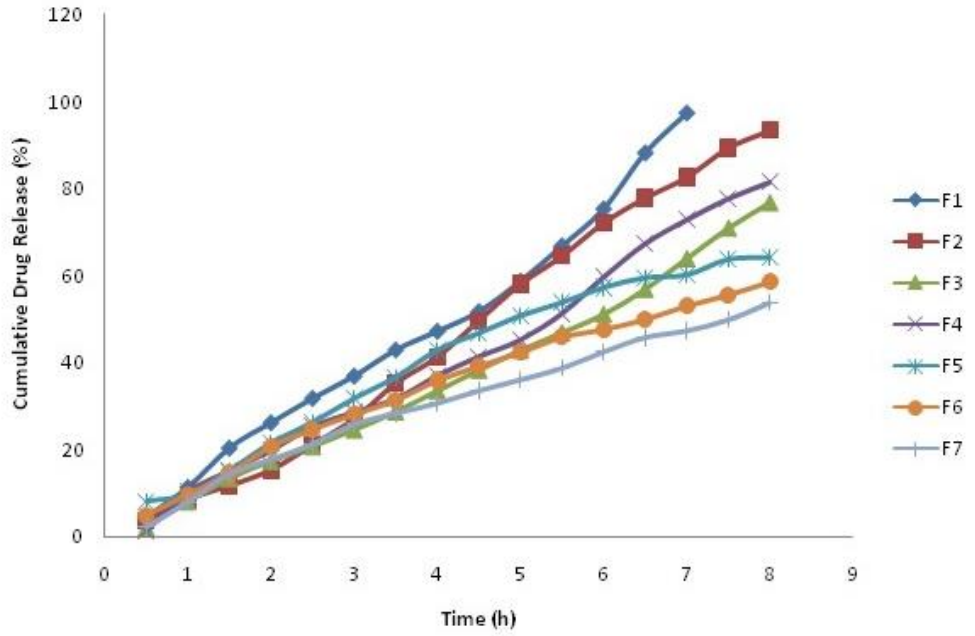

Figure 2 Cumulative drug release profiles of various aceclofenac transdermal patches (Formulations F1 to F7)

Drug release and flux. The formulations F2 to F9 and F11 showed drug release till 8 hours, the maximum study time undertaken. Formulation F2 exhibited the greatest drug release of 93.40 %, while the remaining formulations exhibited lesser drug release. Formulation F9 exhibited the lowest drug release of 41.45 %. Formulations F1, F10, F12 and F13 released 97.22 %, 98.18 %, 98.01 % and 97.6 % in 7, 4, 5, 5.5 h respectively. Hence from the drug release profiles of all formulations F2, showed the best releasing profile 50 % in 4.5 h and 93.40 % in 8 h. This may be attributed to the presence of hydrophobic polymer EC and hydrophilic polymer HPMC in the ratio 3:2. It was noted that the hydrophilic polymer released the drug at faster rate than the hydrophobic polymer.

The cumulative amounts of drug released from formulations F10, F12, and F13 were much higher and faster than formulation F11. The cumulative amount of drug released from formulations containing hydrophilic polymer release drug at faster rate than those containing hydrophobic polymer. Similar results had been observed in the studies by other research groups [5, 22]. Increasing the amount of HPMC (from 100 to 200 and then up to 300 mg) in F1-F3, F4-F6 and F7-F9 reduces the drug release in 8 h study at the same EC level.

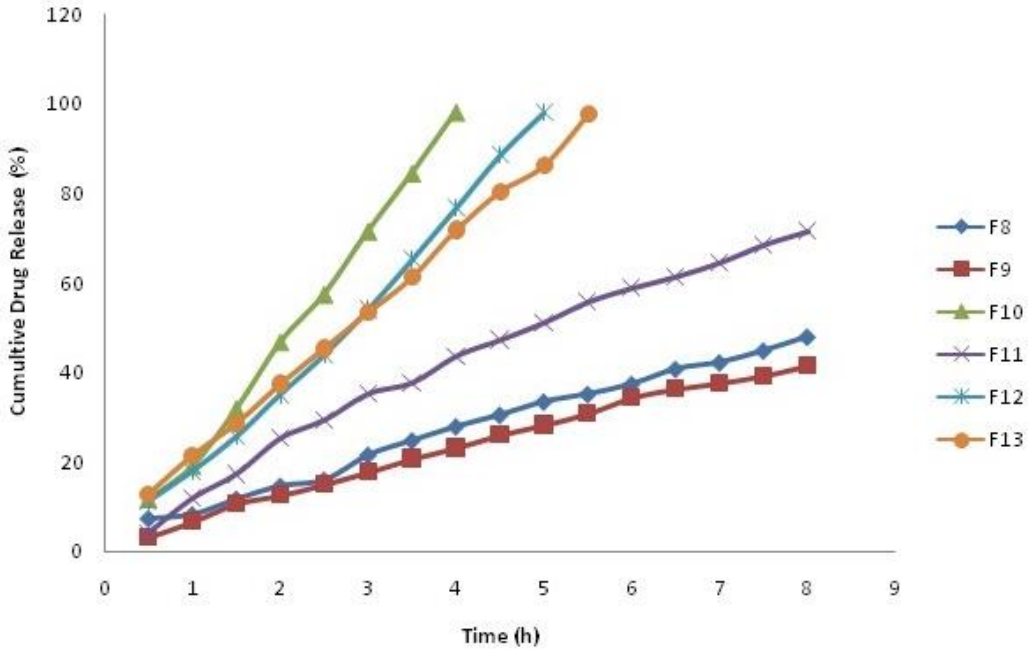

Figure 3 Cumulative drug release profiles of various aceclofenac transdermal patches (Formulation F8 to F13)

Table 3 Regression parameters of various formulations after fitting the drug release data to various release kinetic models

Time	Regression Parameter (R^2 value)					
	F1	F2	F3	F4	F5	F6
Zero Order	0.9816*	0.9785*	0.9883*	0.9887*	0.9465	0.9578
First Order	0.8823	0.8645	0.9237	0.9154	0.9909*	0.9988*
Higuchi	0.7796	0.7470	0.7779	0.7875	0.8941	0.9078
Hixson-Crowell	0.9190	0.9068	0.9486	0.9445	0.9902	0.9942

Time	Regression Parameter (R^2 value)						
	F7	F8	F9	F10	F11	F12	F13
Zero Order	0.9677	0.9723	0.9860	0.9984*	0.9621	0.9921*	0.9945*
First Order	0.9951*	0.9930*	0.9980*	0.8648	0.9945	0.8691	0.9165
Higuchi	0.8954	0.8896	0.8754	0.7712	0.9013	0.7788	0.8472
Hixson-Crowell	0.9920	0.9908	0.9972	0.9135	0.9978*	0.9154	0.9558

* Represent best regression parameter

Formulation F2 showed the highest flux of 154.1µg/cm^2/h among all prepared formulations while formulation F9 showed the lowest flux of 68.48 µg/cm^2/h at 8 h. Formulation F10 showed the highest flux of 323.5 µg/cm^2/h at 4 h. The results followed the same pattern as *in-vitro* drug release. Formulation F2 contained ethylcellulose (300 mg) and an optimum amount of HPMC (200 mg) for the best release and flux characteristics for a controlled release transdermal patch. In F9, which contained the highest amount of both ethylcellulose and HPMC and drug release and flux were observed the minimum. Formulation F10, which was devoid of ethylcellulose, released drug quickly and thus it was unfitted to develop a controlled drug delivery system. HPMC is a rate controlling hydrophilic polymer with its optimum concentration and combined with a hydrophobic polymer at its optimum amount could provide an optimum in controlling drug release in desired 8 hour study. Good drug release and flux characteristics from F2 patch and acceptable physical evaluation parameters like folding endurance, drug loading, swelling index despite lowest moisture content prompted to opt F2 (EC: HPMC; 3:2) the best formulation among all.

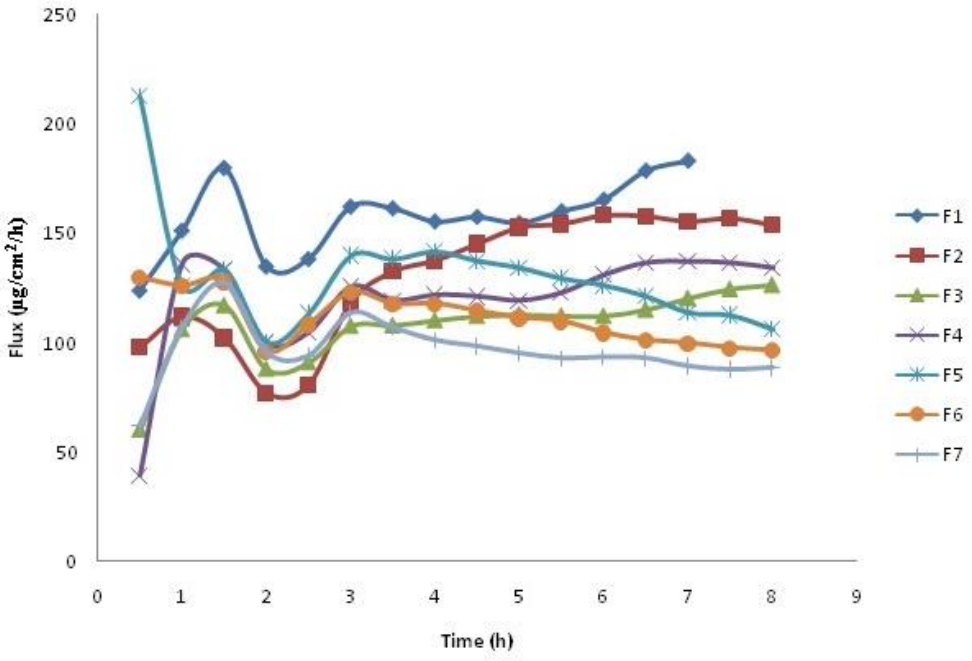

Figure 4 Variation of flux with time in various aceclofenac transdermal patches (Formulation F1 to F7)

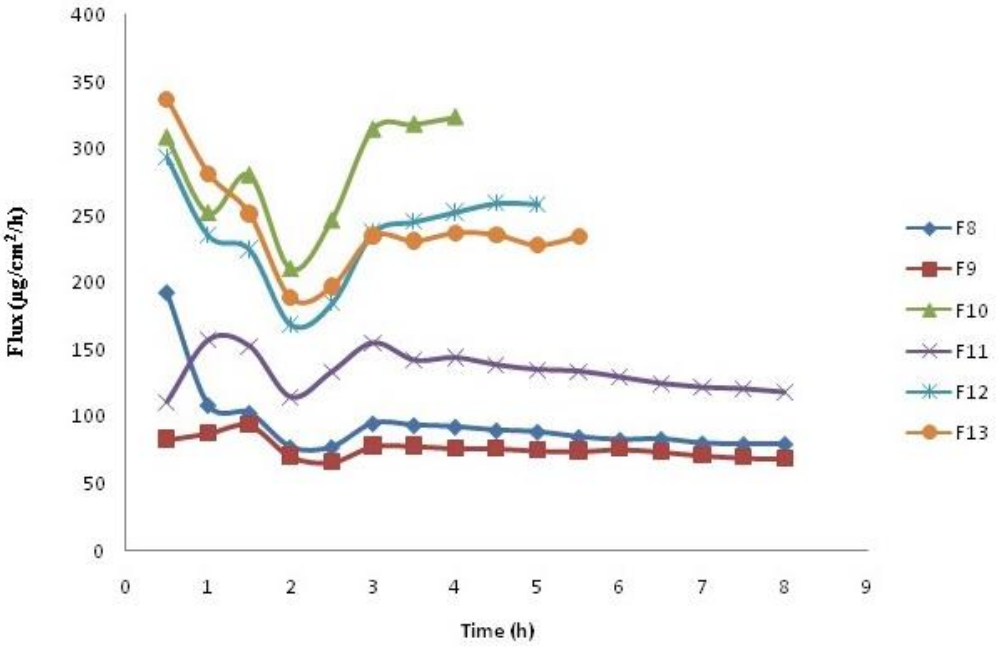

Figure 5 Variation of flux with time in various aceclofenac transdermal patches (Formulation F8 to F13)

*Mathematical modeling of release kinetics***.** The regression parameters obtained after fitting various release kinetic models to the *in vitro* dissolution data are listed in Table 3. After fitting these models to the dissolution data of formulations, the selection was based on comparison of higher determination coefficients. Drug release kinetics for aceclofenac patches F1-F4, F10, F12, and F13 best fitted to the zero order model. For F5-F9, and F11, the best fit model was the first order. Moreover drug releases for F5, F6, F8, F9 were also fitted well to Hixson-Crowell model.

The zero order model described drug release kinetics in the best fitting manner. R^2 (regression coefficient) values for zero order model ranged between 0.9984-0.9465. The Hixson-Crowell model mostly described the drug release data with R^2 (regression coefficient) values ranging from 0.9068 to 0.9978. Generally, the determination coefficients were low for Higuchi model with regression coefficient values of 0.8648-0.9988. The goodness of fit, for various models investigated for aceclofenac transdermal patches, ranked in the order of Zero Order > Hixson-Crowell > First Order >Higuchi according to regression coefficient values.

Drug release was reported to obey the first order kinetics for aceclofenac transdermal patches formulated with polyvinylpyrollidone and ethylcellulose as polymers to prepare the matrix [5]. On the other hand, the release profile of aceclofenac followed the mixed of zero-order and first-order kinetics in different formulations prepared with different ratios of hydrophilic (hydroxyl propyl cellulose) and hydrophobic (ethyl cellulose) polymeric systems [22]. However, in this reported study, 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.

Conclusion

A total of thirteen aceclofenac transdermal patchformulations were prepared. The formulations so developed included transdermal patches of ethyl cellulose, Na-CMC and HPMC. The results so far obtained during this investigation have encouraged us to derive the following conclusions. All prepared formulations showed good physicochemical properties like thickness, weight variation, drug content, swelling index, folding endurance, moisture content. The *in-vitro* release data showed that drug release from different patch formulations have been affected by types of polymers and concentration of polymer. The *in vitro* study results showed that with an increase in the concentration of polymers especially hydrophobic, drug release decreased. Thus formulation F2 (EC: HPMC; 3:2) was considered the best formulation which released 93.40% of total drug in our 8 h study. Furthermore, the F2 formulation exhibited good physicochemical properties and drug release was governed by the zero order kinetics. These 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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