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Formulation of flurbiprofen transdermal patche: *In vitro* and *Ex vivo* report

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ABSTRACT

The main aim of this study was to expand the present formulation with patch and to evaluate the transdermal patches of Flurbiprofen, an NSAID (Non-Steroidal Anti-Inflammatory Drug) used in the treatment of arthritis. Flurbiprofen is required at a sustained rate of its short half- life (3-4 hours) long term percutaneous absorption is required for its gastrointestinal side effects. Hence in this study, an effort was done to develop transdermal patches of Flurbiprofen by employing a different combination of polymers were prepared by the solvent evaporation technique. Nine formulations were prepared consists of Hydroxy Propyl Methyl Cellulose (HPMC) E15 and polyvinylpyrrolidone in the ratios of 1:1, 1:2. Formulation, HPMC E15 and Ethylcellulose (EC) in 1:1, 1:2. Formulations, HPMC E15 and Eudragit RS100 in 1:1, 1:2, and Formulation HPMC E15 and Eudragit RL100 in 1:1, 1:2. Formulations (F1- F8). F9 formulations contain HPMC E15, Eudragit RS100 in 2:1 ratio with permeation enhancer DMSO 20% v/w of propylene glycol was used as a plasticizer in all the formulations. The developed patches were considered for several physicochemical parameters. *In vitro* drug release studies showed maximum percentage in 24 hrs for F9 formulation 94.31±1.43, showed maximum Ex-vivo skin permeation of 10,120±0.91 $\mu g/cm^2$, and the obtained flux meets the required flux. The resultant data was fitted into zero; first, Higuchi and Peppas model and Formulation F9 followed zero order with R_2 0.972. Drug compatibility studies were resulted by FTIR. The results specify that Flurbiprofen transdermal patch can be designed with the required amount of flux with desire mechanical properties for the cause of better therapeutic benefits.

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INTRODUCTION

Transdermal drug delivery systems are designed for the delivery of drug topically at a predetermined and sustained rate. Most promising methods for drug application through the skin and directly to the central compartment are through transdermal drug delivery. It is well-situated route of entry for a variety of drugs. The transdermal patch shows an advanced type of delivery system compared to oral and other routes of administration of its low fluctuation of the drug in the plasma and bypassing hepatic metabolism (Saleem and Idris, 2016). Some drugs show their ability to penetrate the skin when formulated with alcohol for delipidation. Marketed drugs distributed with skin patches include scopolamine, nicotine, oestrogen, nitro-glycerine, and lidocaine to relieve from chronic conditions. Transdermal patches were developed and approved by the Food and Drug Administration, for the treat-

ment of motion sickness (kumar *et al.*, 2010). The superior advantage for transdermal drug delivery was its better bioavailability; regular plasma drug levels and extended duration of therapy due to sustained plasma drug levels compare to low levels of drug with conventional form. The aim of the study is to develop the transdermal patch of Flubriprofen for prolonged action of a drug in the body (Bharkatiya *et al.*, 2010).

MATERIALS AND METHODS

Flubriprofen was supplied as a gift sample from Tocris, New Delhi, India. HPMC 15 cps[23], (Degussa, Germany). Ethylcellulose (Ozone international, Vadodara). Polyvinyl pyrrolidone (ovalikems fine chemical Pvt, Limited., Mumbai). Dichloromethane AR & Methanol (Merck Ltd., Mumbai). Eudragit RS 100, Eudragit RL100 was gifted by (Dr Reddy's laboratories Pvt, Ltd., Hyderabad). Propylene glycol, calcium chloride, aluminium chloride, potassium dihydrogen orthophosphate, sodium hydrogen and dialysis membrane were procured from Hi-Media Mumbai, India.

Preparation of flurbiprofen transdermal films

Patches of Flurbiprofen were designed by solvent evaporation technique, using different ratios of combinations of HPMC E15cps, Ethyl Cellulose, Polyvinyl Pyrrolidine, Eudragit RS 100, and Eudragit RL100. The formulations are done from F1 to F9 using different ratios of polymers, were weighed in required ratios are subjected for continuous stirring over the magnetic stirrer in the solvent mixture of methanol, dichloromethane (1:1) ratio, for about 4 hrs until the polymer gets completely dissolved forming viscous solution which can be kept for swelling for about 2-4hrs. 15% v/w 1,2-propanediol is used as a plasticizer. Then the drug solution was further poured to the solution and cast on anumbra Petri plate of surface area 36.2 sq.cm, allowed for air-dry overnight. The entire patch was fabricated into small patches with the surface area of 4.15sq.cm, and with the diameter of 2.5 cm, about 8 patches was acquired from each sheet. Each patch contains 50 mg of the drug, as shown in Table 1 (Gannu *et al.*, 2007).

Characterization of flurbiprofen transdermal patches

Drug-Excipients compatibility study

FTIR analysis of pure drug (Flurbiprofen), pure polymers and their physical mixture between 400 $cm^{-1}$to 4000 cm^{-1} (Bharkatiya *et al.*, 2010).

Physico chemical properties

The prepared patches by above procedure were conducted evaluated studies (Shah *et al.*, 2011).

Weight variation

Six films from each formulation were weighed individually and the obtained average weight was calculated (Mutalik and Udupa, 2005).

Thickness

The thickness of the films was calculated by using screw gauge at three different points in a film, and average thickness was estimated (Shinde *et al.*, 2008).

Folding Endurance

Folding endurance was measured for formulated batches; it was done manually by repeatedly folding of medicated patch from each batch of three patches at the same place until it breaks. The number of times folded is calculated and average reading is considered (Gaur *et al.*, 2009).

Determination of Drug content in the polymeric films

The designed transdermal films three from each batch were assayed for drug content, and average reading was calculated (Gaur *et al.*, 2009).

Procedure

Films of each formulation are taken, they are cut into small pieces of desired or calculated amount of drug content as 50 mg and dissolved in 100 ml of solution containing its diffusion medium i.e., pH 7.4 phosphate buffer until the drug in the patch gets dissolved. The solution remained diluted with same medium and the absorbance was measured at 247 nm against the blank (Valecha *et al.*, 2011).

Moisture Absorption studies

The formulated patches were accurately weighed and kept in the desiccator, containing saturated solution of aluminium chloride after three days, the patches subjected for weighed. The percentage moisture absorption was calculated with formula (kumar *et al.*, 2010).

% Moisture Absorption =

$$\frac{Final\ weight - \ Initial\ weight}{Initial\ weight} X\ 100$$

% Moisture content

The formulated patches were accurately weighed and kept in a desiccator for containing calcium chloride 24hrs. Then the concluding weight was noted. The percentage of moisture loss from the patch was estimated by the following formula (Liu and Fang, 2015).

Table 1: Composition of Flurbiprofen transdermal patches

Formulations	Drug(mg)	HPMC E15cps: PVP	HPMC E15 cps: EC	HPMC E15 : ERS 100	HPMC E15 cps :ERL 100
F1	50mg	1:1			
F2	50mg	2:1			
F3	50mg		1:1		
F4	50mg		2:1		
F5	50mg			1:1	
F6	50mg			2:1	
F7	50mg				1:1
F8	50mg				2:1
F9	50mg			2:1+ DMSO	

15% v/w1,2-propanediol is used as a plasticizer.
Eachpatch contains 50 mg of Flurbiprofen.
8 patchesare obtained from each sheet.
6% w/w DM SO permeation enhancer

% Moisture content =

$$\frac{Initial\ weight\ -\ Final\ weight}{Initial\ weight} X\ 100$$

In vitro drug release studies

The release studies from formulated patches were carried out by using Franz diffusion cell. Prepared patch was placed between the donor compartments of diffusion cell separated by dialysis membrane. The receptor region comprising of buffer containing magnetic bead, which is operated by magnetic stirrer, for stirring. Periodically1ml of aliquot sample was taken out from the receptor compartment at graded time intervals and same is replaced with phosphate buffer pH 7.4, analysis was done using UV/Visible spectrophotometer at 247 nm against buffer as a reference (Bharkatiya *et al.*, 2010).

Ex-vivo permeation studies

Ex vivo permeation studies are conducted by using Franz diffusion apparatus to forecast the in vivo absorption of the drug. The prepared rat skin was kept between the diffusion cells, with stratum corneum facing the donor compartment. The patch is applied above the stratum corneum (upper side). The upper side of skin was kept in close contact with patch under evaluation test. A dialysis membrane was kept over the patch, to hold the patch firmly. The receiver phase (lower phase) containing 24 ml of buffer stirred at 500 rpm on a magnetic stirrer. The amount of drug transferred was estimated by taking 5ml of the sample at graded time intervals up to 24 hrs, the volume was reloaded with an equal withdrawn volume of buffer. The absorbance was measured at 247 nm spectrophotometrically. The graph was plotted between the Cumulative amounts of drug transferred in μg/cm^{2}against time.

The drug flux (μg/hr/cm^2) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed skin surface (4.15 sq.cm). The target flux can be calculated by the following equation (Mamatha *et al.*, 2010).

$$J_{Target} = \frac{C_{ss}Cl_T BW}{A}$$

'A' characterizes the effective surface area of the transdermal patch (i.e., 4.15 sq.cm), 'BW' the average human body weight of 70 kg. 'C_{ss}' the steady state plasma concentration of Flurbiprofen.'Cl_T' documented total clearance of Flurbiprofen (0.9 lit/hr/kg), the standard flux value of flurbiprofen is 42.8 μg/hr/cm^2, and experimental results is found to be 41.2 μg/hr/cm^2(as shown in Table 8).

Release Kinetics

In vitro release was fitted into different equations to study the release kinetics n (Akram *et al.*, 2018).

Preformulation study

FTIR Compatibility studies

In the FTIR spectra of the pure drug and final formulation was carried out. In practical the characteristic peaks of pure drug, which are there in spectrum of final formulation. It means that there are no cohesive interactions between the drug and other ingredients used in the formulation as shown in Table 2 & Figure 1 and Figure 2.

Development of Flurbiprofen Transdermal films

For the development of films, the transdermal patches were formulated with HPMC E15cps, Ethyl-

Table 2: Drug-Excipients compatibility study FTIR analysis

Characteristic peaks	Drug (frequency, cm^{-1})	Optimized formulation (frequency, cm^{-1})
O-H stretch (carboxylic acid)	3083.48	3077.59
C-F stretch	1058.56	1058.26
C-C stretch (aromatic ring)	1478.49	1477.00
C=O Stretch (carboxylic acid)	1689.82	1721.03

cellulose, polyvinyl pyrrolidone, Eudragit RS100, Eudragit RL100. Many trails are executed by varying the concentrations of the polymer and their combination. The experiment was started by taking single polymers above mentioned and found that HPMC patch was precipitated, Ethyl Cellulose patch was formed too thick while the PVP patch was not formed but using combinations the patches were formed which are smooth, flexible, and transparent. The dose of the drug in each patch was 50 mg, while the whole polymer weight was maintained 3200 mg using HPMC, EC and HPMC, PVP, Eudragit RS100, Eudragit RL100 in the ratios of 1:1, 2:1 (Gannu *et al.*, 2007).

RESULTS AND DISCUSSION

Characterization of flurbiprofen transdermal films

Weight variation test

Weight variation test was conducted by weighing each individual patch (n=3) as results are shown in Table 3. Weight variation of prepared patches is between 93.4±0.86 to 221 ± 0.76. The maximum standard deviation is ±1.04 for formulation F8.

Thickness variation test

The thickness of a patch increased with increase in polymers dilution. The value of thickness varied 1.6 ± 0.75 to 2.3 ± 0.89. The S.D. values were less than 2.0 mm for all formulations, a sign of more uniform patches were shown in Table 3.

Folding endurance number

The folding endurance of different combinations of polymers is shown in Table 3. The patches formulated using HPMC, EC and Eudragit RL 100 are of high mechanical strength with high folding endurance numbers in the range of 92 to 104, whereas the patches made up of HPMC and Eudragit RS 100 are of low of 62 to 68 indicating low mechanical strength.

Drug content estimation in polymeric films

The drug content was measured and is varied from 48.6 mg to 49.8 mg per 4.15 sq.cm, as shown in Table 4.

Moisture Absorption and Moisture content study

The obtained results of moisture content and moisture absorption studies were shown in Table 4 and Figure 3. The moisture content in the patches was ranged from 0.50% to 0.67% for HPMC and EC combinational patches whereas for HPMC and PVP combinational patches it varied from 0.48% to 0.86% and for HPMC and Eudragit RS100 ranged from 0.93% to 1.20%, Whereas for HPMC and Eudragit RL100 it ranged from 0.96% to 0.98% and the % moisture absorption ranges from 0.95% to 2.41% for HPMC and EC combinational patches 1.22% to 2.49% for HPMC and PVP combinational polymers for HPMC and Eudragit RS 100 ranges from 1.27% to 2.92% for HPMC and Eudragit RL 100 ranges from 1.32% to 1.56%. The obtained results shown that the % moisture content and % moisture absorption was more in patches containing HPMC & Eudragit RS 100 polymers. The low % moisture content and low % moisture absorption values indicate the stability of the patches and the presence of little moisture helps the patch from being brittle and completely dried.

In vitro drug release studies

Further show the release profiles of Flurbiprofen from transdermal patches. Formulations F5, F6, F9 showed the greatest percentage of drug release values (83.05±1.95, 85.95±1.95 and 94.31±1.43 mg respectively as shown in the Table 5 and Figure 5) the formulations containing HPMC & Eudragit RS 100 exhibited greater drug release than HPMC and EC, HPMC and PVP, HPMC and Eudragit RL 100 combinational patches. In the current study, it was revealed that the concentration of water-soluble polymers (HPMC, ERS 100), increased the drug release rate also increases rather than the hydrophobic polymers (EC) and other polymers used in the study.

The optimized formulation F9 was fitted into various kinetic models ("zero-order, first-order, Higuchi square root and Korse Meyer peppas model"). The R^2 values of zero-order plot (0.972) was higher than the R^2 values of the first-order plot (0.527), and

Higuchi release kinetics studies R^2 value was 0.885 greater than that of Korse Meyer Peppas model R^2value was 0.696 and follows diffusion process as shown in Table 6. The R^2 values disclose that the drug permeation of Flurbiprofen from the patches followed Zero-order mechanism and R^2 value indicate that the release follows the diffusion process.

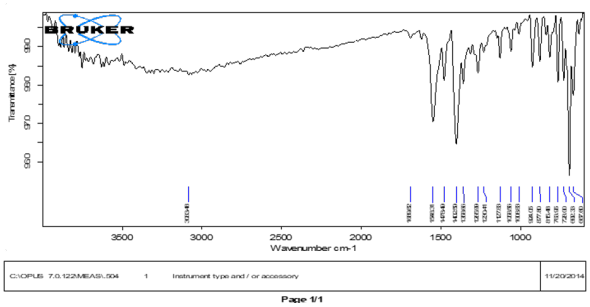

Figure 1: FTIR spectra of puredrug (Flurbiprofen)

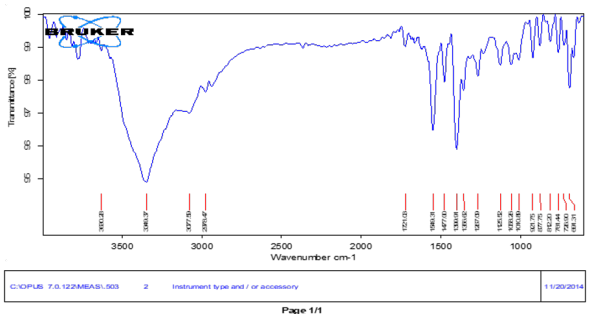

Figure 2: FTIR spectra of final formulation (F9)

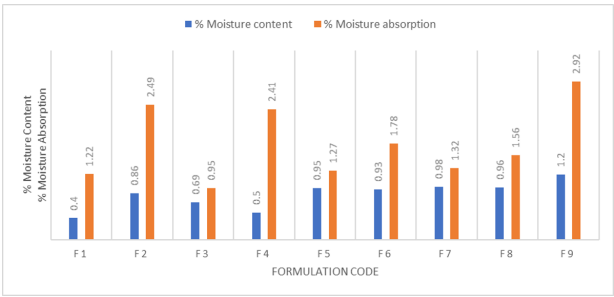

Figure 3: Moisture absorbed and Moisture content of Flurbiprofen transdermal patches, mean ± S.D (n=6)

Kinetic analysis of Diffusion data

In vitro release data was fitted with various release equations and kinetic models like the first order, Zero-order, Higuchi and Korsemeyer Peppas (as shown in Figures 5, 6 and 7, and Figure 8). The formulation F9 drug release data was plotted in these models, and the zero-order equation showed highest linearity (R^2=0.981) followed by Higuchi model (R^2=0.851), so it follows zero-order release pattern indicating diffusion process.

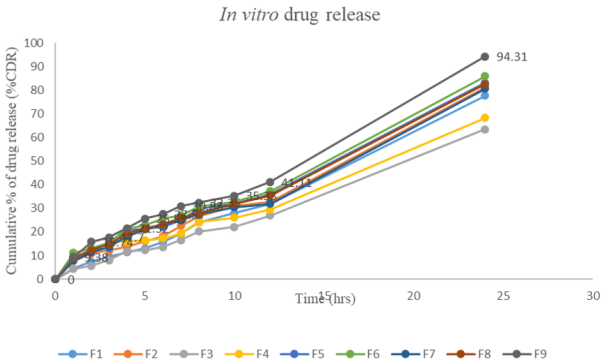

Figure 4: In vitro drug release of Transdermal patch

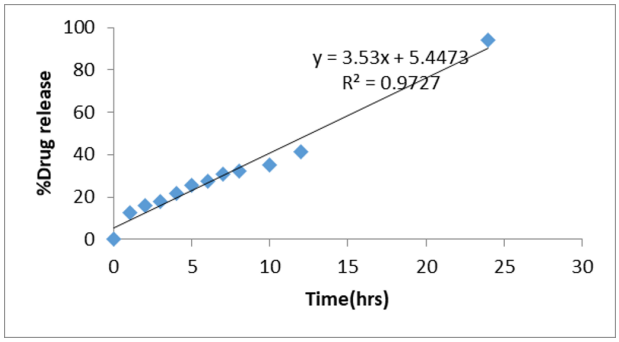

Figure 5: Zero order release kinetics of Formulation F9

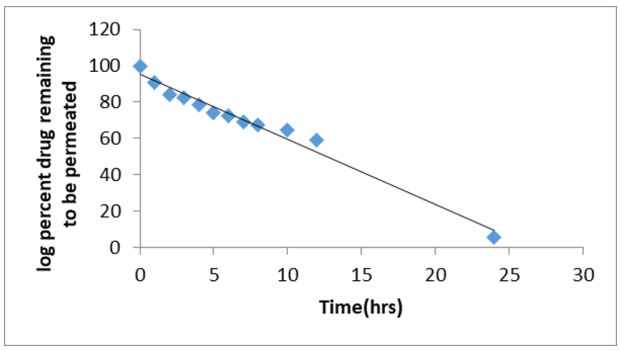

Figure 6: First order release kinetics of Formulation F9

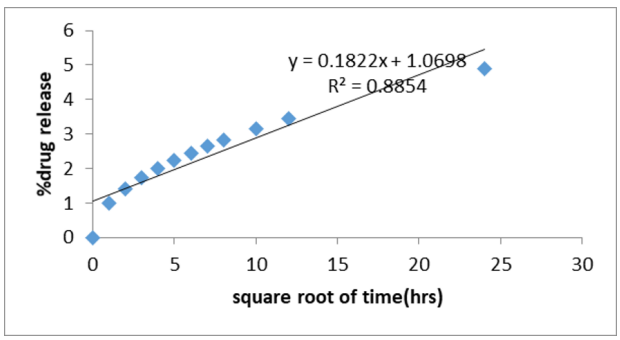

Figure 7: Higuchi release kinetics of Formulation F9

Table 3: Weights, Thickness and folding endurance of Flurbiprofen Transdermal patches

Formulation code	Patch Weight (mg)	Patch Thickness (mm)	Patch endurance	Folding
F1	221±0.76	1.7±0.75	102±3.97	
F2	218.7±0.91	1.6±1.05	97±2.65	
F3	103.9±0.93	1.6±0.75	103±4.73	
F4	99.2±0.67	2.2±0.82	92±5.04	
F5	94.5±0.94	2.3±0.89	62±2.88	
F6	96.3±0.87	2.3±0.75	68±2.9	
F7	93.4±0.86	1.7±1.17	103±2.87	
F8	94.3±1.04	1.8±0.89	93±1.98	
F9	99.6±0.95	1.8±1.52	104±2.01	

Table 4: Drug content, % Moisture absorbed, and % Moisture content of Flurbiprofen patches, mean± S.D (n=6)

Formulation code	Drug content (mg)	%Moisture content	%Moisture absorbed
F1	49.6±0.57	0.4±1.26	1.22±0.49
F2	48.8±0.25	0.86±1.57	2.49±0.44
F3	48.3±0.75	0.69±1.34	0.95±0.38
F4	48.6±0.53	0.50±2.12	2.41±0.47
F5	49.6±0.76	0.95±2.57	1.27±0.32
F6	49.8±0.76	0.93±1.66	1.78±0.65
F7	49.4±0.76	0.98±2.05	1.32±.45
F8	49.6±0.79	0.96±2.07	1.56±0.47
F9	49.8±0.53	1.20±1.05	2.92±0.52

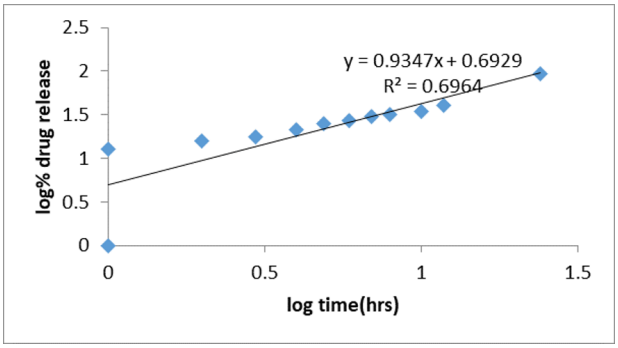

Figure 8: Korse Meyer peppas model of Formulation F9

Ex-vivo permeation studies

The Ex vivo skin permeation studies were done by using skin from albino rats (weighing between 200 to 250 gm). The transdermal patches were safely pressed on the middle of the rat skin surface, and placed above the recipient compartment contains 24 ml of phosphate buffer pH 7.4 as a diffusion medium. Both compartments called as donor and recipient compartments was kept in contact with each other with continuous stirred magnetically during the study. Sample of 5 ml was withdrawn and replaced with equal ml of fresh phosphate buffer pH 7.4 at different time intervals to maintain the sink condition for the entire experimental procedure. (Gannu *et al.*, 2007). The obtained periodical samples were analysed using UV Spectrophotometrically at 247 nm to estimate drug content. Results were shown in Table 7 and Figure 9.

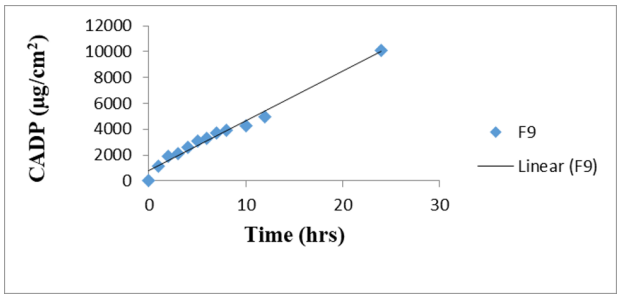

Figure 9: Cumulative amount of drug permeated (CADP) of F9 formulation ($\mu g/cm^2/hr$)

The skin delivery is a novel method to deliver the drug into the blood circulation at a predetermined rate, which not only bypasses "hepatic first-pass

Table 5: In Vitro Release of Flurbiprofen from Transdermal patches

Time (hrs)	% Cumulative Drug released (%CDR) (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	4.48± 1.86	7.58± 1.48	4.39± 1.52	8.43± 1.06	8.12± 1.66	11.1± 1.4	7.86± 1.36	8.89± 1.86	9.38± 1.42
2	7.42± 1.85	10.99± 0.79	5.69± 1.13	11.97± 1.64	12.06± 1.69	13.0± 1.7	11.34± 1.85	12.37± 1.51	15.74± 1.54
3	9.43± 0.95	12.15± 0.77	8.03± 1.76	15.83± 1.96	13.36± 1.87	15.3± 1.5	13.79± 0.95	14.81± 1.72	17.70± 1.83
4	11.34± 1.19	13.81± 1.48	11.79± 1.53	15.92± 1.34	20.77± 1.95	21.4± 1.9	18.19± 1.19	19.27± 1.51	21.52± 1.80
5	13.00± 1.65	16.15± 1.28	12.33± 1.61	16.41± 1.72	21.39± 2.18	22.8± 1.2	21.13± 1.65	21.52± 0.93	25.59± 1.75
6	15.79± 1.25	18.07± 2.07	13.59± 1.62	17.21± 1.78	22.11± 2.44	25.7± 1.5	23.14± 1.25	23.09± 1.75	27.50± 1.43
7	19.12± 1.93	22.60± 1.85	16.55± 1.38	19.37± 1.16	24.85± 2.71	26.9± 1.8	25.05± 1.93	26.03± 1.23	30.88± 1.89
8	24.02± 1.78	26.5± 1.93	20.15± 1.15	24.12± 1.13	29.85± 2.15	30.6± 2.1	27.45± 1.15	28.04± 1.05	32.35± 1.01
10	27.94± 1.15	30.88± 1.37	22.06± 1.52	26.03± 1.32	31.86± 1.74	32.8± 2.3	30.48± 1.63	31.90± 2.10	35.33± 1.55
12	31.86± 1.63	32.84± 1.23	26.96± 1.56	29.51± 1.93	36.02± 1.80	37.2± 2.8	31.9± 1.78	35.38± 1.25	41.11± 1.25
24	77.66± 1.15	81± 1.45	63.46± 1.13	68.36± 1.06	83.05± 1.95	85.95± 1.95	80.60± 1.65	82.58± 1.23	94.31± 1.43

Table 6: Kinetic analysis of Diffusion data's

Formulation Code	Zero order R^2	First order R^2	Higuchi model R^2	Korsemeyer peppas model R^2
F9	0.972	0.527	0.885	0.696

Table 7: Permeation study of flurbiprofen from optimized transdermal patch F9 formulation

Time (hrs)	Cumulative amt of drug permeated ($\mu g/cm^{2)}$ F9
0	0
1	1130.1±3.19
2	1896.8±2.98
3	2133.0±1.65
4	2590.3±3.87
5	3077.1±2.98
6	3306±1.35
7	3725.3±4.18
8	3896.3±4.61
10	4253.01±2.65
12	4951.8±4.11
24	10,120±0.91

Table 8: Q_{24} release, Q_{24} Permeation and J_{SS} of Flurbiprofen Transdermal patch F9 Formulation

Formulation code	Q_{24} permeation (%)	Q_{24}Permeation (μg/ cm^2)	JSS (μg/ hr/ cm^2)
F9	94.31±1.43	10,120±0.91	41.2

elimination" but also to achieve effective drug level in the plasma.

Transdermal patches are designed with matrix type containing flurbiprofen as a drug, prepared by solvent evaporation technique, using three different polymers in different ratios HPMC: PVP in two different ratios 1:1, 2:1 (F1, F2), HPMC: EC in same two ratios 1:1, 2:1 (F3, F4), HPMC: ERS 100 in two different ratios 1:1, 2:1 (F5, F6), HPMC: ERL 100 in two different ratios 1:1, 2:1(F7, F8) Formulations without penetration enhancers and penetration enhancer added to F6 formulation that is 6% DMSO (chemical penetration enhancer) and named as F9 formulation. All formulations contain 15% 1, 2-propane diol as a plasticizer.

Preformulation studies like FTIR and solubility studies are made for drug and excipients mixtures. In the FT-IR spectra, it is observed that the peaks of major functional groups of Flurbiprofen, which are present in the spectrum of pure drug, are same observed but, with a slight difference in the final formulation. It means that there are no interactions between the drug and other ingredients.

The prepared patches were done for evaluation for the following properties such as "Weight variation test, thickness, folding endurance, estimation of drug content, moisture absorption, and moisture content determination, In-vitro release studies and Ex-vivo permeation studies." Results obtained for weight variation test found to be uniform in weight, as evidenced by the highest SD values of 1.04, In thickness estimation test, the thickness was uniform. As the polymer concentration increases the resulted thickness also increased. The generated SD values were found less than 2.0 mm for all formulations, a sign of more undeviating patches. The folding endurance numbers of different combinations of polymers are shown in Table 3. The mechanical ability of the patches can be given by folding endurance number. The patches formulated using HPMC, EC and Eudragit RL 100 are of high mechanical strength with high folding endurance numbers in the range of 92 to 104, whereas the patches made up of HPMC and Eudragit RS 100 are of low folding endurance numbers in the values of 62 to 68 indicating low mechanical strength. From the above results, it is evident that the patches remained rigidity with skin folding when applied and would not break. Drug content was detected in all patches as conformed by low SD values. The actual drug content is ranged from 48.3 mg to 49.8 mg per 4.15 sq.cm, as shown in Table 4.

The results of moisture absorption & moisture content studies were shown in Table 4 and Figure 3. The patches containing moisture was varied from 0.50% to 0.67% for HPMC and EC combinational patches whereas for HPMC and PVP combinational patches it ranged from 0.48% to 0.86% And for HPMC and Eudragit RS100 ranged from 0.93% to 1.20%, Whereas for HPMC and Eudragit RL100 it ranged from 0.96% to 0.98% and the % moisture absorption ranges from 0.95% to 2.41% for HPMC and EC combinational patches 1.22% to 2.49% for HPMC and PVP combinational polymers for HPMC and Eudragit RS 100 ranges from 1.27% to 2.92% for HPMC and Eudragit RL 100 ranges from 1.32% to 1.56%. The results shown that the % moisture content and % moisture absorption was more in patches containing HPMC &Eudragit RS 100 polymers. The low % moisture content and low % moisture absorption values indicate the stability of the patches and the presence of little moisture helps the patch from being brittle and completely dried. Figure 4 further shows the release profiles of Flurbiprofen from transdermal patches. Formulations F5, F6, F9 exhibited greatest percentage of drug release values (83.05±1.95, 85.95±1.95 and 94.31±1.43 respectively) the formulations containing HPMC & Eudragit RS 100 exhibited greater drug release than HPMC and EC, HPMC and PVP, HPMC and Eudragit RL 100 combinational patches. In this study, it was concluded that as the amount of water-soluble polymers (HPMC, ERS 100), and increased the drug release rate rather than the hydrophobic polymers (EC) and other polymers. Cumulative amounts of drug permeated for the optimized formulation was found to be 10,120±0.91 μg/ cm^2 respectively.

The evidence of the similarity factor results in the optimized formulation F9 were subjected into various kinetic models (zero-order, first-order, Higuchi square root and Korsemeyer peppas model). The R^2 values of zero-order data (0.972) was found to be superior than the R^2 values of first-order data (0.527), and Higuchi release kinetics studies R^2

value was 0.885 greater than that of Korse Meyer Peppas model R^2value was 0.696 and follows diffusion process. The R^2 values disclose that the permeation of Flurbiprofen from the transdermal patches obeys zero-order mechanism and R^2 value indicates that the release follows the diffusion process. The above-obtained results of the drug (Flurbiprofen) through the rat abdominal skin confirmed that the formulation is well suitable for human skin (Patel *et al.*, 2011) .

CONCLUSION

Finally, it is decided that the transdermal patches have some novelty in skin administration of Flurbiprofen. All prepared batches showed good Physico-chemical properties like "thickness, weight variation, and drug content". The release data represents that drug release from the patch formulation was dependent upon the diffusion mechanism. Thus, the transdermal patches could provide drug delivery in a controlled rate across undamaged skin.

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