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Permeation Of Flurbiprofen Polymeric Films Through Human Cadaver Skin

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Abstract: Flurbiprofen is a non-steroidal anti-inflammatory drug widely used in the treatment of rheumatism and non arthritic pain. Flurbiprofen is highly gastric irritant and it may produce nausea and vomiting on oral administration, hence a transdermal drug delivery system may be suitable for flurbiprofen. The objective of this study was to formulate and evaluate the transdermal patches of flurbiprofen using synthetic polymers and permeation enhancers. Polymers used were polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) and the permeation enhancers were dimethylformamide (DMF) and dimethylsulfoxide (DMSO). Matrix type transdermal patches of flurbiprofen were prepared by moulding technique. Thin layer chromatography (TLC) of the films prepared showed the same Rf value as that of the pure drug thus it was concluded that no incompatibility between the various components of the patch. The results of skin irritation study showed that no noticeable irritation on rabbit skin indicating the skin compatibility of drug as well as polymer matrix. The uniformity of drug content was evidenced by low S.D values and the thickness of the formulations varied from 0.15 to 0.21 mm. In vitro permeation through human cadaver skin was carried out using modified Franz diffusion cell and the results showed that film (P4) containing PVP and PVA (1:0.5) with DMSO showed the maximum release (83.45%) at 24 hours. The developed transdermal films of flurbiprofen showed promising physico-chemical characteristics and good in vitro drug release.

Keywords: Transdermal, flurbiprofen, anti-inflammatory, dimethylsulfoxide, polyvinyl alcohol, polyvinylpyrrolidone.

INTRODUCTION

Transdermal patch is a medicated adhesive device that is placed on the skin to deliver drugs for systemic effects at a predetermined and controlled rate.[1] The major advantages associated with transdermal drug delivery is, it provides controlled release of drug in to the patient and enables a steady blood level profile, avoidance of first-pass gut and hepatic metabolism, potentially decreased side effects and the rapid termination of therapy in problematic cases.[2] In addition, the dosage form of transdermal patches is patient friendly, convenient and painless and offers multi-day dosing.[3] Transdermal drug delivery systems have been developed for many drugs such as metoprolol[4], ketoprofen[5], propranolol[6], labetolol hydrochloride.[7] Flurbiprofen is a non-steroidal anti-inflammatory drug (NSAID) widely used in the symptomatic treatment of arthritis.[8] Suitable long term percutaneous absorption of flurbiprofen at a controlled rate is needed because of its short half-life (3-4 hours) and gastrointestinal side effects.[9] Hence in the present study an attempt was made to develop transdermal patches of Flurbiprofen by employing

polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) as polymers and polyethylene glycol 400 (PG400) as a plasticizer. Furthermore to improve the skin permeation, dimethylformamide (DMF) and Dimethy sulfoxide (DMSO) were used as permeation enhancers.[10] These formulations were subjected to physico-chemical evaluation and *in vitro* permeation studies.

MATERIALS AND METHODS

Flurbiprofen was received as a gift sample from Knoll Pharma, Goa, India. PVP and PVA were obtained from Central drug house Ltd. Mumbai. PG, DMSO and DMF purchased from Ranbaxy fine chemicals, Mumbai, India. Cadaver skin was procured from Father mullers hospital Mangalore,India. All other materials used were of analytical grade. Drug samples were characterized by UV spectrophotometer.

Formulation of Transdermal patches

In the present study matrix type transdermal patches of flurbiprofen were prepared by moulding technique.[11,12] A flat square shaped moulds having surface area 16cm^2 and height 1 cm were fabricated for this purpose. The casting solutions were prepared by dissolving weighed quantities of polymers (PVP:PVA) in water by heating on a water bath at 50^{0}C. The drug(flurbiprofen) , plasticizer (Poly ethylene glycol 400) and penetration enhancers [Dimethy sulfoxide (dmso), Dimethy formamide(dmf)] were then added to the polymer solution and thoroughly mixed to form a homogeneous mixture and cooled. Entrapped air bubbles were removed by applying vacuum. Casting solution was poured in to glass moulds and were dried at 50 - 55 ^{0}C in hot air oven . The patches were removed by peeling and cut in to square films of 4 cm x 4cm. These patches were kept in desiccator for two days and then wrapped in aluminium foil.

Evaluation of Transdermal patches:

Formulated patches were evaluated for Physico-chemical parameters, In-vitro diffusion, compatibility, stability and skin irritation studies.

Physico- chemical parameters[13,14]

a) Physical appearance

All the patches were visually inspected for colour, flexibility , homogeneity and smoothness.

b) Film thickness[15]

The thickness of the prepared patches were measured at five different places using a screw gauge and mean values were calculated.

c) Weight variation test[16]

Prepared patches were cut in 1 cm^2 pieces and weight of each patch was determined by using digital balance , the average weight of each patch and standard deviation was calculated.

d) Drug content uniformity[17]

Each of the patches used in weight variation test was transferred in to a graduated glass stoppered flask containing about 50 ml of distilled water maintained at 45 – 50 ^{0} C . The flasks were closed and shaken for 4 hours in a mechanical shaker . The solution was filtered , residue washed with distilled water and the filtrate made to required volume and absorbance was measured by UV spectrophotometer at 247 nm. Drug content of each patch was calculated from standard graph.

e) Folding endurance[15]

A small strip of film 2cm x 2cm was subjected to this test by folding the patch at the same place repeatedly several times until a visible crack was observed.

f) Moisture absorption[17]

The percentage of moisture absorption was measured by keeping the patches at 37±0.5°C and 80% ± 5% RH for 2-3 days. Initial weight and final weight of the patches were taken. Percentage moisture absorption was calculated using the formula:

% Moisture absorption

$$= \frac{\text{(Final weight- Initial weight)}}{\text{Initial weight}} \times 100$$

In-vitro permeation studies [18,19]

The in-vitro permeation of the patches were studied using modified Franz diffusion cell. The cell consists of two compartments, the donor and the receptor compartment. The donor compartment was in contact with ambient conditions of atmosphere. The receptor compartment was in contact with phosphate buffer (pH 7.4) and was stirred by a rod shaped magnetic bead driven by a magnetic stirrer at 50 rpm. The patch with a support of backing membrane was kept in the donor compartment and it was separated from the receptor compartment by excised human cadaver skin. The cadaver skin was allowed to keep at room temperature and immersed in distilled water for 10 to 20 minutes before the experiment. The temperature of receptor compartment was maintained at 37 ± 1^oC. Aliquots of the receptor fluid were withdrawn at 2 hours interval up to 24 hours and an equivalent volume of solution was replaced in to receptor compartment with fresh fluid. The samples were analyzed for drug content at 247 nm using UV spectrophotometer.

Thin layer chromatography (TLC)

Compatibility studies are carried out to assess any incompatibility between drug and polymers. The TLC plates having silica gel coating of 0.25 mm thickness were used after activating in an oven for one hour at 120 ^{0}C. A spot of the standard solution was put 2cm from the bottom. The sample solution was spotted 2cms apart from one another and placed in TLC chamber, which was previously saturated with the solvent system chloroform : acetone (4:1). The solvent was allowed to rise at least 3/4th of the plate and the distance travelled by solvent front was noted. The spots were detected by spraying the acidified potassium permanganate ($KMno_4$) on to the plate. The Rf value was calculated for the standard and sample solutions using the formula

$$\text{Rf value} = \frac{\text{Distance travelled by the solute from the origin}}{\text{Distance travelled by the solvent front from the origin}}$$

Stability studies

For any rational design and evaluation of dosage forms the stability of the active component must be a major criteria in determining their acceptance or rejection. Drugs instability is indicated by a change in the physical appearance such as colour, odour, taste or texture of the formulation where as in other instances chemical changes may occur which are not self evident and may only be ascertained through chemical analysis. To assess the stability of the formulated transdermal patches, selected films were taken. The stability studies were carried out at room temperature over a period of 60 days. The patches were evaluated for physical characteristics and drug content at regular intervals of time.

Primary skin irritation studies

The skin irritation study was carried out by using healthy rabbit. The hair of rabbit was shaved from the dorsal area on both sides 24 h before the test, one side of the back serves as control for the test. The medicated patch was secured on experimental side, and the non-medicated patch was secured on the control side. Then the patches were removed after 24 h and the condition of the dorsal skin was examined visually. The evaluation was based on scoring method described by Draize, where the scores are assigned from 0 to 4 based on the severity of erythema or oedema.[19]

RESULTS AND DISCUSSION

In the present study altogether nine (9) formulations were prepared by varying the polymer ratio and permeation enhancers. The formulated patches were subjected to various physico-chemical evaluations and in vitro permeation study. The physicochemical characteristics of the formulated patches are showed in Table 2. The films showed uniform drug content and minimum batch variation. The thickness of the patches varied from 0.15 to 0.21 mm. The minimum standard deviation values assured that the process used for preparing the delivery system was capable of giving reproducible results. A good uniformity of weight was observed in all the films prepared. Folding endurance was high (>200) thus assuring good flexibility of the films and were able to maintain the integrity with general skin folding. Moisture uptake capacity increased with increase in concentration of PVP which can be supported by previous reports. PVP might enhance the absorption of water vapour by converting the crystalline drug in to amorphous state on skin surface. Compounds in the amorphous state generally posses a high energy state with improved solubility and the enhancement of solubility of drug close to the skin surface increases thermodynamic activity that facilitates the permeation rate of drug through skin.[12] The in vitro permeation studies through cadaver skin showed that the addition of enhancers promoted the permeation of drug. Among the permeation enhancers used, DMSO showed better permeation efficacy than DMF. It was observed that, the patch (P4) prepared with polymer ratio (PVP:PVA, 1:0.5) and DMSO as the permeation enhancer had the maximum drug release of 83.45 % at the end of 24 hours. The release rate of flurbiprofen from film preparations tend to increase as the PVP fraction is increased. A proposed mechanism for DMSO to improve skin permeation of drugs is, it denature the protein and on application to human skin has shown to change the intercellular keratin conformation.[10]

The Rf value of flurbiprofen was 0.318 and for the formulated patch was found to be 0.309. TLC of the prepared patches had almost same Rf value as that of the drug, which shows that the drug and polymers are compatible with each other. Skin irritation was studied by modified draize test and the results showed no noticeable irritation on rabbit skin, indicating the skin compatibility of drug as well as polymer matrix. Stability studies were conducted on the selected formulation (P4) and results shown in Table 3. It was observed that no significant change occurred in physical appearance, thickness, weight, folding endurance, % elongation, tensile strength and drug content. Based on these results it can be concluded that the formulated patches were physically and chemically stable.

Table 1: Composition of Flurbiprofen Transdermal Patches.

Formulation code	Drug (%)	Polymer Ratio		Penetration enhancer (%)	
		PVP	PVA	DMSO	DMF
P1	20	1.0	0.5	-	-
P2	20	0.5	1.0	-	-
P3	20	0	1.5	-	-
P4	20	1.0	0.5	10	-
P5	20	0.5	1.0	10	-
P6	20	0	1.5	10	-
P7	20	1.0	0.5	-	10
P8	20	0.5	1.0	-	10
P9		0	1.5		10

All formulations carried 20% w/w PEG 400 as plasticizer.

Table 2: Physico-chemical parameters of the formulated patches

Formula tion code	Thickness* (mm)	Weight Variation*(mg)	Folding endurance	% Moisture absorption*	Drug content* (mg/cm^2)
P1	0.154 ± 0.031	18.07 ± 0.025	>200	4.4 ± 0.429	3.981 ± 0.056
P2	0.198 ± 0.025	19.83 ± 0.028	>200	3.6 ± 0.396	4.00 ± 0.038
P3	0.203 ± 0.030	19.95 ± 0.038	>200	3.2 ± 0.431	3.980 ± 0.0511
P4	0.163 ± 0.025	20.03 ± 0.042	>200	4.1 ± 0.629	3.987 ± 0.032
P5	0.206 ± 0.024	21.36 ± 0.022	>200	3.6 ± 0.440	4.027 ± 0.046
P6	0.210 ± 0.027	21.68 ± 0.025	>200	3.4 ± 0.552	3.948 ± 0.035
P7	0.158 ± 0.034	20.30 ± 0.038	>200	4.0 ± 0.730	3.974 ± 0.036
P8	0.205 ± 0.028	20.96 ± 0.036	>200	3.5 ± 0.593	4.020 ± 0.028
P9	0.209 ± 0.022	21.05 ± 0.032	>200	3.3 ± 0.542	4.026 ± 0.054

*Data are expressed as mean ± S.D (n=3)

Table 3: Stabilities studies on a selected patch*

Day	Physical appearance	Thickness* (mm)	Weight variation* (mg)	Folding endurance	% Moisture absorption *	Drug content* (mg/cm^2)
0 day	Smooth and flexible	0.162 ± 0.022	20.03 ± 0.030	>200	4.0 ± 0.326	3.987 ± 0.054
15th	No significant changes	0.163 ± 0.031	20.10 ± 0.035	>200	4.2 ± 0.401	3.981 ± 0.038
30th	No significant changes	0.163 ± 0.025	20.15 ± 0.033	>200	4.2 ± 0.229	3.948 ± 0.051
60th	No significant changes	0.164 ± 0.020	20.25 ± 0.038	>200	4.2 ± 0.213	3.892 ± 0.032

*Data are expressed as mean ± S.D (n=3)

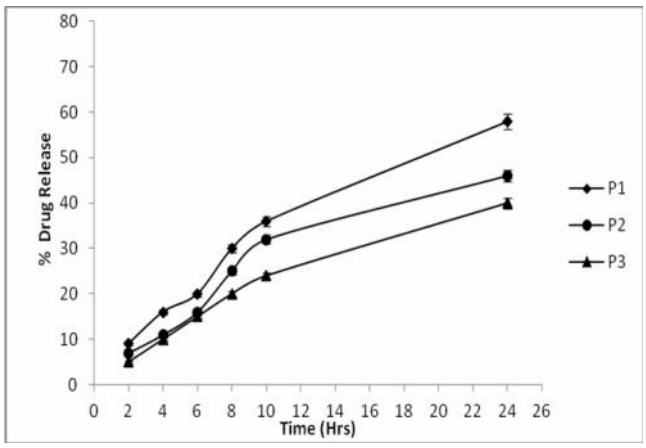

Fig. 1 *In vitro* drug permeation through human cadaver skin
Data are expressed as mean ± S.D (n=3)

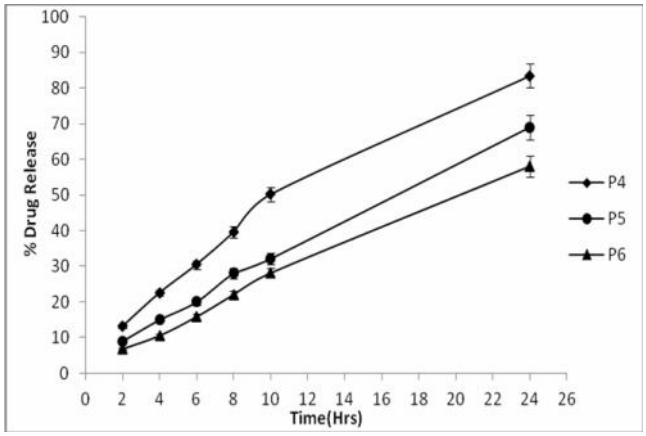

Fig. 2 Effect of DMSO on *in vitro* drug permeation
Data are expressed as mean ± S.D (n=3)

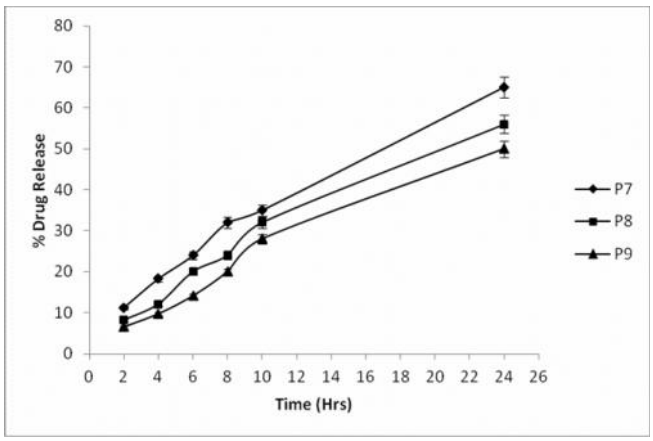

Fig. 3 Effect of DMF on *in vitro* drug permeation
Data are expressed as mean ± S.D (n=3)

CONCLUSION

To avoid the extensive first-pass metabolism and achieve the desirable penetration rate of flurbiprofen, transdermal patches were prepared by employing PVP and PVA as film former, and PEG as a plasticizer. It was concluded that film (P4) containing PVP:PVA(1:0.5) with 10% w/w DMSO as the permeation enhancer successfully improved the skin penetration of flurbiprofen.

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