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Original Article

PHYSICOCHEMICAL EVALUATION OF TRANSDERMAL PATCHES CONTAINING THE DRUG FLUFENAMIC ACID .

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INTRODUCTION

Transdermal drug delivery systems (TDDSs) is a self- contained distinct dosage forms which delivers the drug by means of transdermal patch through the epidermis of the skin at a predetermined and sustained rate with low biological half life. It provides systemic delivery of drug through increased bioavailability with reduced dosing frequency. The skin has a number of considerable advantages over other routes of administration when used as a site of drug delivery, including increased patient compliance, the ability to avoid gastric irritation, no hepatic first-pass metabolism thus enhancing the bioavailability, minimize the risk of systemic side effects by reducing plasma concentrations contrast to oral therapy, provide a sustained release of drug at the site of application; rapid termination of therapy by removal of the patch, the reduction of fluctuations in plasma levels of drugs, and avoid pain associated with parenterals. Thus TDDS has the potential of reducing side effects and improving patient compliance. [3]

Flufenamic acid is chemically 2-Amino- 2-(hydroxymethyl)-1,3-propanediol (S)-3- benzoyl-alpha-methylbenzeneacetate. The structure of Flufenamic acid is shown in Figure 1. [4]

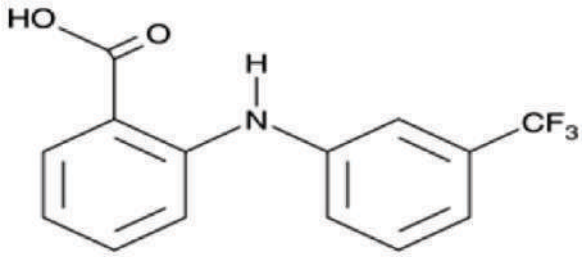

Fig. 1: Structure of Flufenamic acid

It belongs to a class of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). It is used as an analgesic and anti-inflammatory drug. It works by blocking the action of cyclo-oxygenase in the body, which is involved in the production of prostaglandins in the body. Prostaglandins are produced in response to injury or certain diseases and may cause swelling, inflammation and pain. By blocking cyclo-oxygenase, it prevents the production of prostaglandins and therefore reduces inflammation and pain. [5]

The motive of the present work was to formulate and characterize the transdermal patches of Flufenamic acid in order to investigate the practicability of this route of administration for prolonged action of drug in body and also increase the patient compliance and bioavailability.

1. Materials and Methods

Materials

Flufenamic acid was received as a generous gift sample from Emcure Pharmaceuticals Limited, Pune, India.

HPMC, Ethyl Cellulose and Eudragit RS 100 were procured from S. D. Fine Chemicals, Mumbai, India. Dialysis membrane was purchasedfrom Hi-Media Laboratories Ltd., Mumbai, India. All other laboratory chemicals and reagents used in the study were of either pharmaceutical analytical grade.

METHODS

1. Preformulation studies of drug.
2. Identification of drug.

Organoleptic properties

Color, odor, taste, and state were determined.

Determination of melting point

The melting point was determined by the capillary method. The temperature at which the drug melted was recorded.

Determination of UV absorption maxima

The identification of drug was done by UV spectrophoto- metric method. From the spectra, λ_{max} of Flufenamic acid was observed at 288 nm. The spectral data from this scan was used for the preparation of a calibration curve Flufenamic acid. [6]

Fourier transform infrared analysis

FTIR analysis of the sample was employed for compound identification (FTIR-8400S Shimadzu). The powdered drug was scanned from 400 to 4000 cm^{-1}.

Determination of solubility

The solubility analysis for Flufenamic acid was done by solubility determination in different solvents like Water, Chloroform, DMSO, Ethanol, etc.

Determination of partition coefficient

The partition coefficient was determined by dissolving 10 mg of drug in separating funnels containing 10 ml portion of each of n-Octanol and PBS pH 7.4. The separating funnels were shaken on mechanical shaker for 24 hours. Two phases were separated and aqueous phase was filter through Whatman filter paper and the amount of the drug in aqueous phase was determined spectrophotometrically at 288 nm. [7]

Calibration of flufenamic acid

Stock solution was prepared by dissolving 100 mg of Flufenamic acid in 100 ml phosphate buffer in a volumetric flask. An aliquot of desired concentration was prepared. The absorptivity coefficient of the drug at the 288 nm was determined.

Drug- excipients 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 interact ions between the drug and other ingredients used in the formulation.

3.Formulation of Flufenamic Acid Transdermal Patches:

The ethyl cellulose (1.50 gm) and diethyl phthalate were dissolved and mixed together in ethyl acetate (40 ml). Diethylphthalate is used as a plasticizer. The PVP powder was completely dissolved in ethanol (10 ml) and the drug was dispersed uniformly in the solution with continuous stirring. Then, these solutions were homogeneously mixed by a mechanical stirrer. The mixture solution was sonicated for 30 min to reduce the air bubbles. Then, the mixture solution was poured into Petri-dish with area 70.88 cm^2 and dried in hot air oven at 50 ± 2°C for 5 hrs. The dry Flufenamic acid matrix patches were peeled-off from Petri-dish and kept in a desiccator until used for physical characterization.

Table 1: Composition of Flufenamic acid transdermal patches

S. No.	Formulation Code	Drug (g)	PVP K30 (g)	PVP K90 (g)	Drug PVP Ratio	Diethyl phthalate (g)
1.	F1	0.38	-	-	-	0.45
2.	F2	0.38	0.76	-	1 : 2	0.68
3.	F3	0.38	0.95	-	1 : 2.5	0.74
4.	F4	0.38	-	0.57	1 : 1.5	0.62
5.	F5	0.38	-	0.76	1 : 2	0.68

4.Physicochemical Evluation Of Flufenamic Acid Patches:

Physical Appearance:

All formulated transdermal patches were visually inspected for colour, clarity, entrapment of any air bubble, flexibility and smoothness, which on a large part determines patient acceptability of the patch and also therapeutic efficacy. [177]

Thickness:

Thickness of transdermal patch was measured by using digital thickness gauge (Muttato Japan). Thickness of rectangular patch (2x2 cm) was determined with a four different points and average thickness was taken. Same was performed for other patches also. [178]

Weight Variation:

Weight variation study of transdermal patches was performed by individually weighing 10 randomly selected patches on digital weighing balance and average weight was calculated. The individual weight of patches should not deviate significantly from the average weight. [179]

Drug Content:

The designed transdermal films three from each batch were assayed for drug content, and average reading was calculated. [180]

Films of each formulation are taken, they are cut into small pieces as 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 288 nm against the blank. [181]

Moisture Content:

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 [182]

$$\% \text{ Moisture content} = \frac{Final\ weight - nitial\ weight}{Initial\ weight} \times 100$$

The formulated patches were accurately weighed and kept in a desiccator for containing calcium chloride 24 hrs. Then the concluding weight was noted. The percentage of moisture loss from the patch was estimated by the above-mentioned formula. [183]

Moisture Uptake:

Transdermal patches were kept in desiccators at room temperature for 24 h with silica geland weighed (Ws) and transfer to other desiccators to expose of 75% RH using a saturated solution of sodium chloride at 25°C and patches were reweighed again and again, until a constant weight (Wm) was obtained. The moistureuptake capacity was calculated according to the given formula [184]

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% Moisture uptake =

(Wm – Ws) / Ws x 100

Flatness:

Longitudinal strips from the 5 randomly selected transdermal films of each formulation were cut out. One from the center and one from the other side of patch. The length of each strip was measured and the variation in length because of the non-uniformity of flatness was measured. 0 % constriction was considered to be 100 % flatness. Flatness was calculated by measuring constriction of strip using given formula [185]

% Constriction =

(I1 – I2) / I2 100

Where,

I1 = Initial length of each strip,

I2 = Cutted film length

Folding Endurance:

The folding endurance of patch was expressed as the number of folds (number of times the patch folded at the same place), either to break the preparation or to develop visible cracks. This test was performed to determine the stability of sample to withstand folding and brittleness. Folding endurance of patches was determined by repeatedly by folding a small strip of patches (approximately 2×2 cm) at the same place till it broke. The number of times patches could be folded at the same place, without breaking gave the value of folding endurance and it was recorded. [186]

Tensile Strength:

The formulated patches were evaluated for its tensile strength to measure their mechanical properties. The tensile strength of the patches were determined by using a self designed assembly. Assembly consists of a pan hanged by using a strong thread and the other end of the thread was attached with the centre of the patch. The whole assembly was held like a beam balance and weights were kept on the pan. Weights required to break the patch was noted. Tensile strength was then calculated using the following formula [16]

Tensile Strength = Break Force / a . b (1 + ΔL/L)

Where,

a = Width of the patch,

b = Thickness of the patch

L = Length of the patch,
ΔL = Elongation of patch at break point

Break Force = Weight required to break the patch (Kg)

Thumbtack Test

One week after the preparation of transdermal patches, the thumb was lightly put into contact for a short time (10 secs.) and then with drawn quickly by varying the pressure and time of contact and noting the difficulty of pulling the thumb from the adhesive, it was possible to perceive how easily, quickly and strongly the adhesive can form a bond with the skin. It is the most simple and straight forward test for the evaluation of the adhesive skin bonding. The adhesion properties were expressed by the following value range; good adhesion, poor adhesion and no adhesion. [188]

5.Result And Discussion

Physicochemical Eveluation Of Flufenamic Acid Patches:

The prepared transdermal patches were evaluated for their physiochemical characteristics like physical appearance, thickness, weight uniformity, drug contents, moisture contents, moisture uptake, flatness and folding endurance.

Physical Appearance:

The formulated patches were found to be clear, smooth, uniform, flexible in their physical appearance and free from entrapment of air bubble.

Thickness:

Table 6.22: Thickness of different batches of Flufenamic acid patches:

S. No.	Formulation Code	Thickness (mm)
1.	F1	0.273 ± 0.014
2.	F2	0.254 ± 0.017
3.	F3	0.266 ± 0.008
4.	F4	0.276 ± 0.010
5.	F5	0.261 ± 0.022

The thickness of different batches were found in range from 0.254 to 0.276 mm.

Weight Variation:

Table 6.23: Weight Variation of different batches of Flufenamic acid patches:

S. No.	Formulation Code	Weight Variation (mg)
1.	F1	164.87 ± 2.08
2.	F2	169.61 ± 1.48
3.	F3	167.19 ± 1.88
4.	F4	166.72 ± 1.92
5.	F5	165.20 ± 1.69

The weight of transdermal patches varied from 164.37 to 169.61 mg which indicated that the prepared different batches of transdermal films were similar in weight.

Drug Content:

Table 6.24: Drug Content of different batches of Flufenamic acid patches:

S. No.	Formulation Code	Drug Content (%)
1.	F1	96.25 ± 0.42
2.	F2	97.26 ± 1.42
3.	F3	94.12 ± 0.74
4.	F4	94.38 ± 0.92
5.	F5	97.64 ± 1.04

No significant difference in drug content was observed in all the formulated patches which were found in range from 94.12 to 97.64%.

Moisture Content:

Table 6.25: Moisture Content of different batches of Flufenamic acid patches:

S. No.	Formulation Code	Moisture Content (%)
1.	F1	1.996 ± 0.010
2.	F2	2.298 ± 0.014
3.	F3	2.114 ± 0.021
4.	F4	2.310 ± 0.024
5.	F5	2.450 ± 0.026

The moisture content in the patches was ranged from 1.9% to 2.4%.

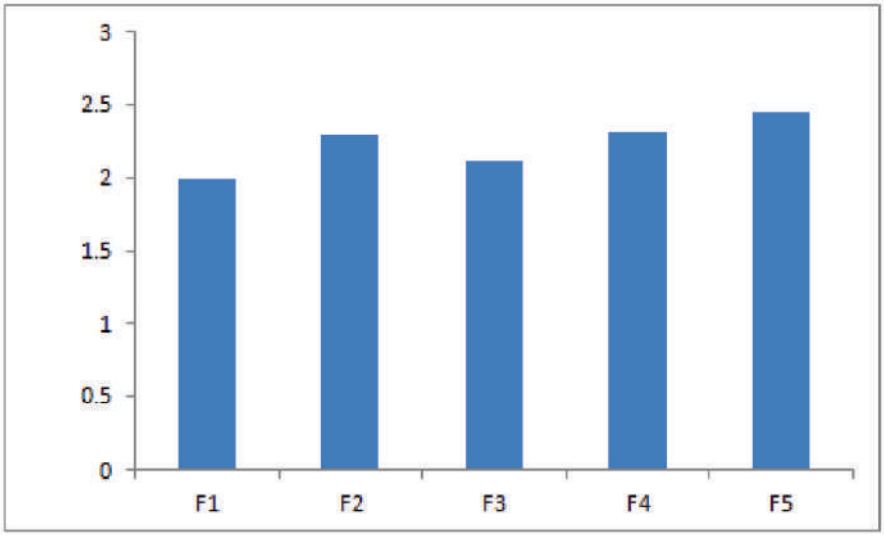

Figure 6.53: Percentage of moisture content from Flufenamic acid patches

Moisture Uptake:

Table 6.26: Moisture Uptake of different batches of Flufenamic acid patches:

S. No.	Formulation Code	Moisture Uptake (%)
1.	F1	4.21 ± 0.03
2.	F2	4.04 ± 0.03
3.	F3	5.12 ± 0.07
4.	F4	5.04 ± 0.03
5.	F5	5.93 ± 0.05

The % moisture uptake ranged from 4.04% to 5.93%.

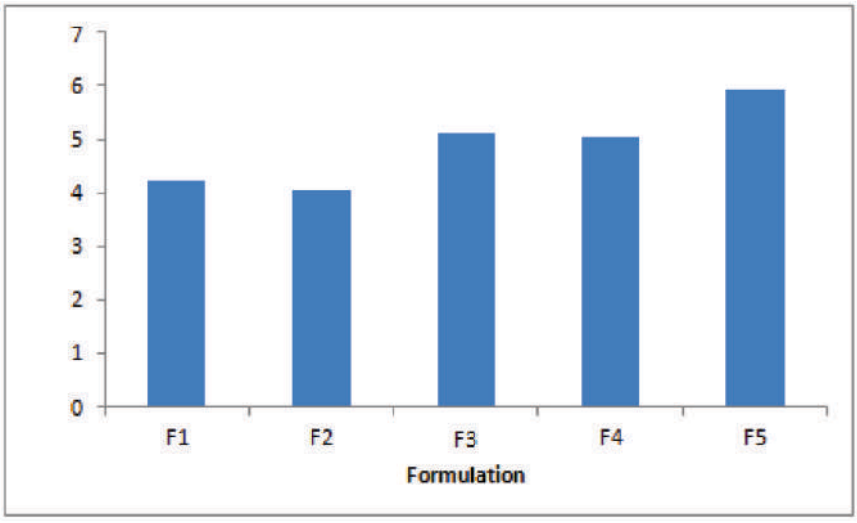

Figure 6.54: Percentage of moisture uptake from Flufenamic acid patches

Flatness:

Table 6.27: Flatness of different batches of Flufenamic acid patches:

S. No.	Formulation Code	Flatness (%)
1.	F1	100
2.	F2	100
3.	F3	100
4.	F4	100
5.	F5	100

Flatness studies were performed to determine the formulation construction. 100 % flatness of all the formulated patches indicated that there was no amount of constriction in formulated transdermal patches. Thus, formulated transdermal patches could better maintain a smooth surface when applied onto the skin.

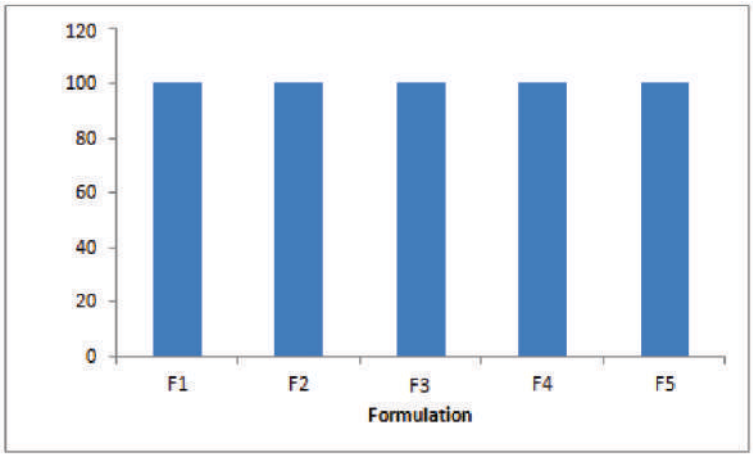

Figure 6.55: Flatness of Flufenamic acid patches

Folding Endurance:

Table 6.28: Folding Endurance of different batches of Flufenamic acid patches:

S. No.	Formulation Code	Folding Endurance
1.	F1	42 ± 4.08
2.	F2	46 ± 6.50
3.	F3	44 ± 3.43
4.	F4	39 ± 4.69
5.	F5	48 ± 5.12

The folding endurance determines the ability of patch to withstand rupture. It was measured manually. The Folding Endurance ranged from 42 to 48 for the transdermal patch. The result indicated that the patches of all batches would not break and would maintain their integrity with general skin folding when used.

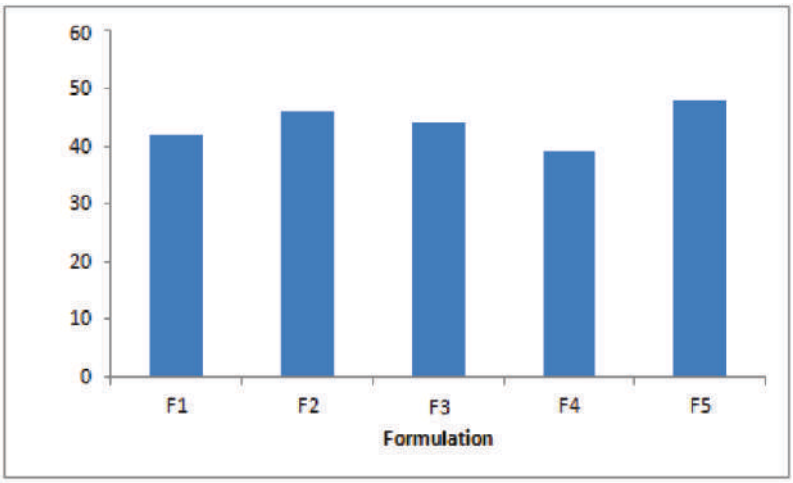

Figure 6.56: Folding Endurance of Flufenamic acid patches

Tensile Strength:

Table 6.29: Tensile Strength of different batches of Flufenamic acid patches:

S. No.	Formulation Code	Tensile Strength (kg/mm^2)
1.	F1	0.316 ± 0.020
2.	F2	0.372 ± 0.030
3.	F3	0.386 ± 0.055
4.	F4	0.346 ± 0.050
5.	F5	0.473 ± 0.036

Tensile strength of transdermal patches are important since they are expected to be sufficiently flexible and to have a mechanical strength on skin for a long period of time. Tensile strength results showed that strength of films were in a range from 0.316 to 0.473kg/mm^2.

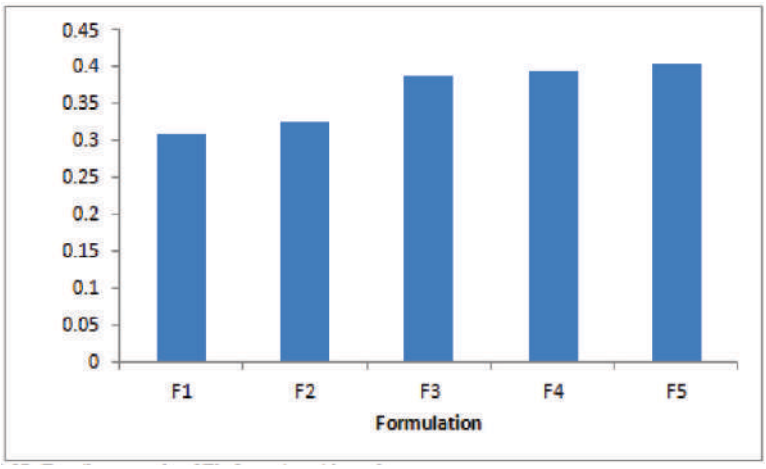

Figure 6.57: Tensile strength of Flufenamic acid patches

Thumbtack Test:

Table 6.30: Adhesive property of thumbtack test of Flufenamic acid patches

S. No.	Formulation Code	Thumbtack Test
1.	F1	Good adhesion
2.	F2	Good adhesion
3.	F3	Good adhesion
4.	F4	Good adhesion
5.	F5	Excellent adhesion

Formulations F5 showed excellent adhesion in Thumbtack Test.

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