Asian Journal of Pharmaceutical Education and Research
Vol -10, Issue-4, October- December 2021
ISSN:2278 7496

RESEARCH ARTICLE Impact Factor: 7.014

FORMULATION DEVELOPMENT AND EVALUATION OF TRANSDERMAL PATCHES OF FENOPROFEN

Murli*, Kaushelendra Mishra, Dr. A. K. Singhai

Lakshmi Narain College of Pharmacy (LNCP), Bhopal (M.P.)

*Corresponding Author's E mail: mrmurli532@gmail.com

Received 12 July 2021; Revised 18 July 2021; Accepted 05 Aug. 2021, Available online 10 Oct. 2021

Cite this article as: Murli, Mishra K, Singhai AK. Formulation Development and Evaluation of Transdermal Patches of Fenoprofen. Asian Journal of Pharmaceutical Education and Research. 2021; 10(4): 109-118.

https://dx.doi.org/10.38164/AJPER/10.4.2021.109-118

ABSTRACT

The objective of this study is to prepare and evaluate Fenoprofen transdermal patches by using different combinations of polymer and enhancers as well as compare the efficiency of various enhancers. Transdermal patches composed of different polymers HPMC, Ethyl Cellulose, Eudragit RLPO and Eudragit RSPO. The thickness of the films varied from 85±3 to 105±4 mm. All the patches showed satisfactory folding endurance properties. Folding endurance values of all formulation more than 185 indicating good elasticity and strength. The formulation F2 show lowest moisture content and moisture uptake than other formulation. This is due to because of polymer ratio (like Ethyl Cellulose). If lower moisture content in transdermal patch it be good to prevent the brittleness with 100% dryness and also maintain the stability of formulation. The tensile strength was found to be in the range of 0.891 to 0.995. The formulation Fenoprofen F3 showed the best tensile strength. The *In-vitro* permeation study was done to see the effect of polymers through the Franz diffusion cell from patch having Eudragit RLPO, RSPO, HPMC, EC in different conc. to optimized formulation for in-vitro study.

Keywords: Fenoprofen, Transdermal patches, Ethyl Cellulose, Eudragit RLPO, Eudragit RSPO, Formulation, Evaluation.

INTRODUCTION

The skin plays an important role in the transdermal drug delivery system. The skin of an average adult body covers a surface area of approximately 2 sq. m. and receives about one third of the blood circulating through the body and serves as a permeability barrier against the transdermal absorption of various chemical and biological agent. The main three layers of skin play an important role in transdermal drug delivery system[1-2]. Transdermal permeation is based on passive diffusion. Before a topically applied drug can act either locally or systemically, it must penetrate the stratum corneum – the skin permeation barrier. In the initial transient diffusion stage drug molecules may penetrate the skin along the hair follicles or

sweat ducts and then absorbed through the follicular epithelium through the intact stratum corneum becomes the primary pathway for transdermal permeation[3]. These are the compounds, which promote skin permeability by altering the as a barrier to the flux of a desired penetrant and are considered as an integral part of most transdermal formulations. To achieve and maintain therapeutic concentration of drug in the blood, the resistance of skin to diffusion of drugs has to be reduced in order to allow drug molecules to cross skin and to maintain therapeutic levels in blood. They can modify the skin's barrier to penetration either by interacting with the formulation that applied or with the skin itself [4].

The penetration enhancer should be pharmacologically inert, non toxic, non-allergenic, non-irritating and ability to act specifically, reversibly and for predictable duration. It should not cause loss of body fluids, electrolytes or other endogenous materials. Transdermal patch (Skin patch) uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), and lidocaine to relieve the pain of shingles (herpes zoster). Molecules of insulin and many other substances, however, are too large to pass through the skin. Patches applied to the skin eliminate the need for vascular access by syringe or the use of pumps. Transdermal patches were developed in the 1970s and the first was approved by the FDA in 1979 for the treatment of motion sickness. It was a three-day patch that delivered scopolamine. In 1981, patches for nitroglycerin were approved, and today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol, oxybutinin, scopolamine, and testosterone. There are also combination patches for contraception, as well as hormone replacement. Depending on the drug, the patches generally last from one to seven days.

Non-steroidal anti-inflammatory drugs (NSAIDs) are amongst the most widely used therapeutic class of analgesic compounds used to relieve post extraction pain. The selection of transdermal drug delivery system (TDDS) is advantageous as it can maximize the rate of transfer of drug into systemic circulation and can also reduce its time of stay in the skin tissues if properly formulated with some permeation enhancers. The metabolism of drug, that is primary factor in oral delivery system, is markedly minimized by administering the drug through skin. For efficient transdermal drug delivery system, the drug must be able to penetrate the skin barrier and reach the target site. Transdermal patches are also responsible for the sustained release of drug through skin into the blood stream. Hence, NSAIDs patches not only remove above mentioned side effects but also improve the patient compliance, avoid first pass effect and maintain a controlled release of drug. Fenoprofen is a nonsteroidal anti-inflammatory drug. Fenoprofen is used for

symptomatic relief for rheumatoid arthritis, osteoarthritis, and mild to moderate pain. The objective of this study is to prepare and evaluate Fenoprofen transdermal patches by using different combinations of polymer and enhancers as well as compare the efficiency of various enhancers.

MATERIALS AND METHODS

Material

Fenoprofen was received as a generous gift sample from pharmaceutical company. Colorcon Asia Pvt. Ltd., Mumbai, India was the chief supplier for HPMC E15 and ethyl cellulose. Methanol was purchased from Himedia Laboratories India, Mumbai, India. All other chemicals and reagents used in the study were of analytical grade.

Methods

Preparation of blank patches:

Accurately weighed polymers taken in combination and dissolved in respective solvent (chloroform and methanol in the ratio of 1:1 v/v) then poured in petridish with glycerin on plain surface. Then film was dry over night at room temperature.

Preparation of rate controlling membrane

Eudragit RLPO and RSPO were used for the preparation of rate controlling membranes. Polymers were dissolved in chloroform and methanol with PEG 600 as plasticizer. Then solution was then poured into a glass Petri dish. The solvent was allowed to evaporate under room temperature for 24 hrs[5].

Preparation of matrix type transdermal patches

Transdermal patches composed of different polymers HPMC, Ethyl Cellulose, Eudragit RLPO and Eudragit RSPO[6]. The polymers were dissolved in chloroform and methanol along with plasticizer. Then the solution was poured into a glass Petri dish containing Glycerine. The solvent was allowed to evaporate under room temperature for 24 hrs.

The polymers (total weight: 500 mg) and drug (20 mg) were weighed in requisite ratios and dissolved in 10 ml of chloroform and methanol and PEG 400. After vortex then the solution was poured on glycerin placed in a glass Petri dish and dried at room temperature for 24 hrs.

Table 1: Preparation of matrix type transdermal patches

Formulation Code	Drug (mg)	HPMC (mg)	RLPO (mg)	RSPO (mg)	Ethyl cellulose (mg)	Total polymer weight (mg)	Plasticizer % w/w of total polymer PEG 6000 (m)l	Permeation Enhancer % w/w of total polymer (Methanol, chloroform) ml
F1	100	400	100	-	-	500	0.5	10
F2	100	300	150	-	50	500	0.5	10
F3	100	200	200	-	100	500	0.5	10
F4	100	400	-	100	-	500	0.5	10
F5	100	300	-	150	50	500	0.5	10
F6	100	200	-	200	100	500	0.5	10

Evaluation parameters

The prepared transdermal films were evaluated for the following parameters:

Microscopic evaluation

An optical microscope (Olympus-Cover-018) with a camera attachment (Minolta) was used to observe the shape of the prepared Transdermal patch for all formulation.

Thickness

The thickness of films was measured by Vernier calipers. The thickness of patches were measured at three different places and average of three readings was taken with standard deviation[7].

Folding endurance

This was determined by repeatedly folding one film at the same place until it broken. The number of times the film could be folded at the same place without breaking / cracking gave the value of folding endurance[8].

Tensile strength.

Cut the patch at the centre having 2cm length and 2cm breadth. Patch was hanged on top and lower side of instrument, then start the switch and note the reading on screen. The thickness and breadth of strips were noted at three sites and average value was taken for calculation[9].

$$Tensile\ strength\ (s) = \frac{Applied\ Force}{Cross\ section\ area}$$

Where, S = tensile stress in 980 dynes/cm2

m = mass in grams

g = acceleration due to gravity (980 dynes/cm2)

b = breadth of strip in centimeters

t = thickness of strip in centimeters

Percentage of moisture content

The prepared patches were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs[10]. Individual films were weighed. The percentage of moisture content was calculated as the difference between final and initial weight with respect to initial weight.

Percentage of moisture uptake

Firstly weighed the patches and then kept in a desiccators at room temperature for 24 hrs and then its exposed to 84% RH (A saturated solution of potassium chloride) in a desiccators. The % of moisture uptake was calculated by difference between final and initial weight with respect to initial weight.

Drug content analysis

The patches (n = 3) of specified area (6.16cm^2) were taken into a 10 ml volumetric flask and dissolved in methanol (10ml) with the help of shaker. After the vortex the solution was filtered and prepared subsequent dilutions and analyzed by UV spectrophotometer at 276 nm[11].

***In vitro* skin permeation study**

The in vitro skin permeation study was done by using a Franz diffusion cell (receptor compartment capacity: 80 ml: surface area: 3.14 cm^2. The egg membrane was separated and used for in vitro study. The receiver compartment was filled with 40 ml of phosphate buffer, pH 7.4. The Transdermal patch was firmly pressed onto the centre of the egg membrane and then the membrane was mounted on the donor compartment[12-13]. The donor compartment was then placed in position such that the surface of membrane just touches the receptor fluid surface. The whole assembly was kept on a magnetic stirrer with suitable rpm throughout the experiment using magnetic beads. The temperature of receptor compartment was maintained at 37± 0.5ºC.

RESULTS AND DISCUSSION

The thickness of the films varied from 85±3 to 105±4 mm. The values obtained for all the formulations are given in the table 2. The folding endurance was found to be in the range. The thickness was

approximately close to every formulation. It depends on polymer ratio. All the patches showed satisfactory folding endurance properties. Folding endurance values of all formulation more than 185 indicating good elasticity and strength table 2.

The moisture content was determined by keeping patches in a desiccators containing activated silica. The percentage moisture uptake was calculated as the difference between initial and final weight with respect to final weight. The results of the moisture content studies for different formulations are shown in Table 3. The formulation F2 show lowest moisture content and moisture uptake than other formulation. This is due to because of polymer ratio (like Ethyl Cellulose). If lower moisture content in transdermal patch it be good to prevent the brittleness with 100% dryness and also maintain the stability of formulation. If formulation content higher moisture it can lead the microbial contamination during the storage of patches. The tensile strength was found to be in the range of 0.891 to 0.995. The formulation Fenoprofen F3 showed the best tensile strength. The values for all the patches are tabulated in the table 3.

The prepared patch showed good tensile strength and there was no cracking sign in patch. There was an increase in tensile strength with an increase in Eudragit RLPO in polymers ratio. The drug content ranged between 97.45±0.45 and 99.12±0.65. The percentage drug content of all formulations is shown in Table 4.

This test is essential to check the uniformity of drug content in different patches from a single batch. The drug content analysis of patch show that the process employed to prepared patch was capable of giving uniformity drug content and minimum batch variability. F2 is optimized formulation that shows the good result. The *in vitro* permeation studies are prediction of *in vivo* performance of a drug. These studies were performed for different formulations across egg membrane using phosphate buffer, pH 7.4 as an *in vitro* study fluid in the receptor compartment of Franz diffusion cell. The results of these studies are given in Tables 6.

The *In-vitro* permeation study was done to see the effect of polymers through the Franz diffusion cell from patch having Eudragit RLPO, RSPO, HPMC, EC in different conc. to optimized formulation for in-vitro study. All the formulation was studied and all data fitted on Zero Order, First Order to explain the diffusion mechanism and pattern Table 7. The % cumulative drug release was calculated over the study time range in 0-12 hrs. Data analysis for order of release kinetics the formulation followed zero order release kinetics. From the in-vitro permeation study it was confirmed that the release of formulation F3 was to be found higher as compared to other formulation (F1, F2, F4, F5, F6).

Table 2: Thicknesses and folding endurance of different formulations

Formulation Code	Thickness* (µm)	Folding Endurance* (Times)
F1	85±3	189±4
F2	92±5	210±3
F3	105±4	220±5
F4	85±6	195±6
F5	92±5	219±6
F6	98±2	235±3

*Average of Three determinations (n=3, Mean ± S.D.)

Table 3: % Moisture content and moisture uptake of different formulations

Formulation Code	% Moisture content*	% Moisture uptake*
F1	7.85±0.25	3.32±0.22
F2	6.65±0.32	2.25±0.32
F3	5.25±0.14	1.85±0.14
F4	6.58±0.25	4.15±0.16
F5	6.05±0.65	3.36±0.36
F6	6.21±0.11	2.54±0.21

*Average of Three determinations (n=3, Mean ± S.D.)

Table 4: Tensile strength of different formulation

Formulation code	Tensile strength (kg/cm^2)	% Drug content
F1	0.685	97.45±0.45
F2	0.712	96.65±0.23
F3	0.715	99.12±0.65
F4	0.668	98.58±0.45
F5	0.695	98.74±0.25
F6	0.732	98.65±0.22

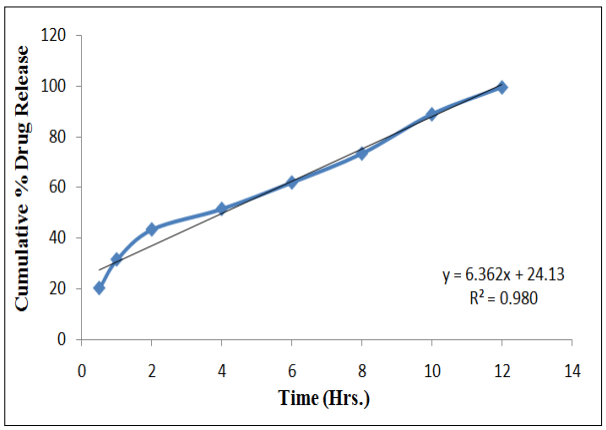
*Average of Three determinations (n=3, Mean ± S.D.)

Table 5: *In Vitro* % permeation profile of fenoprofen in formulation F1-F6

Time	% of Drug Release						
(hr)	F1	F2	F3	F4	F5	F6	Pure Drug
0.5	25.65	23.32	20.14	26.65	23.36	22.12	45.65
1	39.98	35.65	31.45	42.23	39.98	35.56	88.98
2	46.65	42.21	43.32	59.98	49.95	48.85	98.69
4	55.56	53.32	51.45	69.98	55.78	53.32	-
6	78.89	65.58	61.87	83.32	81.47	79.95	.-
8	98.85	89.98	73.32	98.85	96.65	95.12	-
10	98.98	99.58	88.85	98.79	98.98	98.85	-
12	98.99	99.72	99.47	99.25	99.12	99.74	-

Table 6: *In-vitro* drug release data for optimized formulation F3

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	20.14	1.304	79.86	1.902
1	1	0	31.45	1.498	68.55	1.836
2	1.414	0.301	43.32	1.637	56.68	1.753
4	2	0.602	51.45	1.711	48.55	1.686
6	2.449	0.778	61.87	1.791	38.13	1.581
8	2.828	0.903	73.32	1.865	26.68	1.426
10	3.162	1	88.85	1.949	11.15	1.047
12	3.464	1.079	99.47	1.998	0.53	-0.276



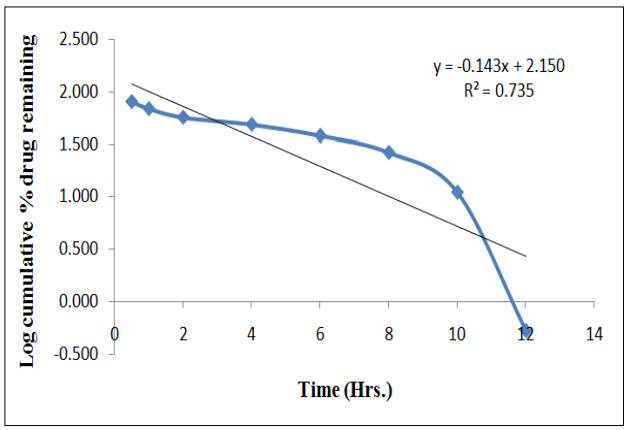


Figure 1: Cumulative % drug released Vs Time **Figure 1: Cumulative % drug released Vs Time**

Table 7: Regression analysis data of fenoprofen transdermal patches

Batch	Zero Order	First Order
		r^2
F3	0.980	0.735

CONCLUSION

In the present study, an attempt was made to deliver a novel anti-hypertensive drug, Fenoprofen through Transdermal route in the form of Transdermal patches. Transdermal patches of matrix were prepared out of which matrix type of patches was found to be satisfactory. Among the different formulations of matrix type (F1 to F6); the formulation F3 containing Eudragit RLPO and HPMC was selected as best formulation. The drug permeation profile was also found to follow zero order kinetics. The patches were thin, flexible and transparent. The Present study showed that matrix Transdermal patches of Fenoprofen exhibited better in vitro performance than pure drug.

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