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Research Article

FORMULATION AND EVALUATION OF DEXIBUPROFEN TRANSDERMAL PATCHES USING VARIOUS POLYMERS

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ABSTRACT

The aim of present investigation on Transdermal patches of Dexibuprofen was formulated by solvent casting method by using the polymers hydroxy propyl methyl cellulose(HPMC) : poly vinyl pyrrolidone (PVP), methyl cellulose (MC): PVP, HPMC: Carbopol 940P, HPMC: methyl cellulose (MC) and Carbopol 940P alone employing poly ethylene glycol (PEG) 400 as plasticizer and dimethyl sulphoxide (DMSO) as permeation enhancer. The prepared formulations were evaluated for physiochemical parameters such as weight variation, thickness, folding endurance, flatness test, Tensile strength, % moisture content, % moisture uptake, drug content. I*n-vitro* drug release was studied by Franz diffusion cell using cellophane as diffusion membrane, skin irritation test was performed on albino rats. There are no significant changes in the physiochemical evaluations except % moisture. The formulation containing hydrophilic polymers shows little moisture content than other formulations. The formulations prepared with HPMC: PVP and HPMC: MC as polymers showed best release than other combinations due to the hydrophilic nature of the polymer. The skin irritation studies using albino-rats revealed no signs of erythema or oedema, which confirms the skin compatibility of the formulated transdermal patches.

Keywords: Transdermal Patch, Dexibuprofen, HPMC, MC, PVP, Skin Irritation Study.

INTRODUCTION

Transdermal therapeutic systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug (s), through the skin, at a controlled rate to the systemic circulation [1]. Transdermal drug delivery uses the skin as an alternative route for the delivery of systematically acting drugs. Transdermal patches control the delivery of drugs at controlled rates by employing an appropriate combination of hydrophilic and lipophilic polymers. Millions of people take NSAIDs every day for arthritis, acute injury, and menstrual cramps. It is estimated that more than 100,000 Americans are hospitalized and between 15,000 and 20,000 die each year from ulcers and gastrointestinal bleeding related to NSAID use [2]. So the objective becomes focused that formulating Dexibuprofen as transdermal patches reduces its dose and dose frequency as well ability to consistently administer the drug at a zero order rate and availability to remove the drug rapidly from the user and in cases of adverse effect, toxicity or any other undesirable effects. An additional advantage is increase in patient compliance. Controlled release and efficient bio availability through transdermal patches may result with lowering the dose required per day. Dexibuprofen is chemically 2S-2-[4-(2-ethylpropyl) phenyl] propionic acid. It is used in the treatment of rheumatoid arthritis, osteoarthritis and

other musculo-skeletal disorders, simple analgesic and antipyretic in lower dose and dental pain having biological half life 1.8- 3.5 hr. the recommended dosage is 600-700 mg per day at 2-3 divided doses [3, 4]. Due to short biological half life and frequent administration of Dexibuprofen make it a potential candidate for sustained release preparations. The aim of the present investigation was to prepare Dexibuprofen patches to produce the systemic and sustained effect for the treatment of inflammation associated pain.

MATERIALS AND METHODS

Dexibuprofen was obtained as gift sample from was obtained from shasun drugs and chemicals Pvt. Ltd. HPMC K4M, MC, PVP K-30, and Carbopol 940P was purchased from sisco research laboratories. All other chemicals and reagents used were of analytical grade. In order to conduct animal studies the institutional animal ethical clearance was obtained.

Preparation of casting solution

The casting solutions were prepared by dissolving weighed quantities of polymers in a solvent mixture of chloroform and methanol in 1:1 ratio. The drug, plasticizer and permeation enhancers were then added to the various polymer solutions individually and thoroughly mixed to form a homogeneous mixture (Table 1). It was placed aside without any disturbances to allow the entrapped air to bubble out. In the present study, matrix type of Transdermal patches of Dexibuprofen was prepared by moulding techniques. A flat circular glass moulds having 2 cm heights and 2cm diameter was fabricated for this purpose.

Preparation of Transdermal patches

About 3ml of casting solutions were pipette out into circular glass moulds especially designed to hold contents, which is casted on mercury surface. The glass moulds containing the casting solutions were allowed for drying at room temperature for 24hrs and the patches were dried in oven at 40-45 ˚C for 30min in order to remove the residual solvents. The patches were removed and cut into square shapes with 2×2 cm^2. These patches were wrapped in a aluminium foil and stored in desiccators for further studies [5-8].

PHYSIOCHEMICAL EVALUATION

Weight variation

As weight variation between the formulated patches was carried out by weighing 6 patches of each batch in an electronic balance and average weight was calculated [9].

Thickness

The thickness of the patches was determined by measuring the thickness at random sites on the formulated patches using optical microscope and the average thickness was determined [10].

Folding endurance

Folding endurance of the patches was determined by repeatedly folding a small strip of patch (2cm×2cm) at the same space till it broke. The number of times, the film could be folded at the same place without breaking, gave the value of folding endurance [10].

Flatness test

3 longitudinal strips are cut from each film at different portion like one from the centre other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction.

Percentage of constriction = $L_1-L_2 / L_2 \times 100$
L1=Initial length of strip
L2=Final length of strip
Flatness=100% of constriction

Tensile Strength and Percentage Elongation

The instrument, which was designed in our laboratory, was used for the measurement of tensile strength One end of the films was fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights were gradually added to the pan to increase the pull force till the film was cut. The elongation was determined simultaneously by noting the distance traveled by the pointer, before break of the film, on the graph paper. The weight required to break the film was noted as the break force. The tensile strength was calculated using Allen's formula.

Tensile strength = $F /a\times b (1+ \Delta L / l)$
F=force required to break
a=width of film
b = thickness of film
ΔL =length of film
l=elongation of film at break point.

Moisture content

The prepared patches were cut into 20x 50 mm strips, weighed individually, and kept in a desiccators containing calcium chloride at 37°c for 24 hours. The films were reweighed individually until a constant weight was obtained. Percentage of moisture content was then calculated based on the change

in the weight with respect to initial weight film [11].

Determination of drug content

A formulated patches was cutted into small pieces and transferred into a graduated glass stoppered flask, which contained 100ml of mixture of chloroform and methanol in the ratio of 1:4, maintained at 45-50˚C. It was closed and subjected to stirring under magnetic stirrer until the homogenous solution was obtained. The solution was filtered and the amount of drug present in the filtrate was determined by using *ANALYTICAL TECHNOLOGY SOLUTIONS* UV spectrophotometer at 222nm. Similarly, blank solution was prepared using a dummy patch. The procedure was carried out in duplicate to determine the drug content [12].

***In-vitro* drug release studies**

In vitro permeation studies were performed by using Franz diffusion cell. It consists of a donor compartment and a receptor compartment. The cellulose membrane was mounted between the donor compartment and receptor compartment of the diffusion cell. The formulated transdermal patches were placed over the semi-permeable membrane, then the receptor compartment was fixed, so that the semi-permeable membrane was in contact with the medium of 50ml of phosphate buffer [pH 7.4]. The contents of the receptor compartment was agitated by a magnetic stirrer at a speed of 45 rpm at room temperature.1ml of the samples was collected at predetermined time interval from the receptor compartment over a period of 24hours,after each sampling equal volume of fresh media was replaced. The amount of drug release from the patch at different time intervals was determined by measuring the absorbance by UV spectrophotometer at 222nm. The cumulative percentage release of drug permeated per cm^2 of patches was plotted against time [9, 13].

Skin irritation test

The patches were tested for their potential to cause skin irritation sensitisation in rats. The rats were divided into 7 groups, on the previous day of the experiment; the hair on the back side area of rat was removed. The animals of group - I were served as control without any treatment. Group –II was taken as standard irritant (formalin - 0.8%v/v). Remaining groups III, IV, V, VI, and VII were taken as test. Transdermal systems were applied on to nude skin of animals. The animals were applied with new patch/formalin solution each day at same time for 7 days and finally the application sites were observed and graded according to a draize scoring scale [11].

Table 1. Formulations of Dexibuprofen transdermal patches

Ingredients	Patch-I	Patch-II	Patch-III	Patch-IV	Patch-V
Dexibuprofen (mg)	10	10	10	10	10
Hydroxy Propyl Methyl Cellulose K4M in parts	0.35	-	0.35	-	0.25
Carbopol 940P in parts	-	-	0.15	0.5	-
Methyl cellulose in parts	-	0.5	-	-	0.25
Polyvinyl pyrrolidone K-30 in parts	0.15	0.2	-	-	-
Polyethylene glycol 400 in ml	16.5	16.5	16.5	16.5	16.5
DMSO in ml	15	15	15	15	15
Solvent system Chloroform: Methanol	1:1	1:1	1:1	1:1	1:1

RESULTS AND DISCUSSION

Table 2. Physico - Chemical evaluation of Dexibuprofen Transdermal Patches (I-V)

S.No	Formulation Code	Weight Variation (mg cm^{-2})	Thickness (µm)	Folding Endurance	Flatness
1	Patch-I	1.62 ± 0.45	169 ± 0.76	115 ± 4. 11	100 ± 0.01
2	Patch-II	1.32 ± 0.25	154 ± 0.65	125 ± 4.23	100 ±0.01
3	Patch-III	1.69 ± 0.49	161 ± 0.72	93 ± 3.94	100 ± 0.01
4	Patch-IV	1.78 ± 0.51	258 ± 0.95	97 ± 3.97	100 ± 0.01
5	Patch-V	1.37 ± 0.29	187 ± 0.82	109 ± 4.01	100 ± 0.01

Table 3. Physico - chemical evaluation of Dexibuprofen Transdermal Patches (I-V)

S.No	Formulation Code	Moisture Content (%)	Moisture Uptake (%)	Tensile Strength (Kg cm^{-2})	Elongation (%)	Drug Content (%)
1	Patch-I	3.12 ± 0.45	8.92 ± 0.58	1.34 ± 0.15	1.0 ± 0.10	95.86 ± 1.45

2	Patch-II	4.23 ± 0.51	4.31 ± 0.45	1.25 ± 0.10	1.3 ± 0.12	89.71 ± 0.09
3	Patch-III	7.84 ± 0.55	3.78 ± 0.41	0.97 ± 0.09	0.9 ± 0.09	88.66 ± 0.07
4	Patch-IV	8.63 ± 0.68	3.14 ± 0.39	0.92 ± 0.09	0.7 ± 0.09	89.35 ± 0.09
5	Patch-V	3.54 ± 0.49	8.71 ± 0.54	0.89 ± 0.08	0.9 ± 0.09	98.48 ± 1.12

Table 4. Cumulative percentage release of Dexibuprofen Transdermal patches

S.No	Formulation Code	Cumulative percentage release of drug at										
		1 hr	2hr	3hr	4hr	5hr	6hr	7hr	8hr	9hr	10hr	24hr
1	Patch-I	4.6	6.2	10.2	12.1	14.4	16.0	18.2	24.5	28.2	30.8	85.7
2	Patch-II	2.6	6.0	8.07	9.96	11.6	12.9	14.5	16.6	19.5	21.6	74.7
3	Patch-III	1.77	2.69	3.23	3.85	4.55	7.47	8.40	9.25	10.2	11.1	25.9
4	Patch-IV	1.59	2.01	2.60	3.28	4.12	4.62	5.38	6.47	7.15	8.49	23.7
5	Patch-V	3.8	5.9	8.51	11.4	14.4	15.3	18.0	19.9	27.3	31.2	83.5

Table 5. Skin irritation studies of Dexibuprofen Transdermal Patches I-V

S.No	Formulation Code	Observation						
		1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
1	Patch-I	0	0	0	0	0	0	0
2	Patch-II	0	0	0	0	0	0	0
3	Patch-III	0	0	0	0	0	0	0
4	Patch-IV	0	0	0	0	0	0	0
5	Patch-V	0	0	0	0	0	0	0
6	Formalin[0.8%]	0	1	1	2	2	2	2

Figure 1. Cumulative % release of Dexibuprofen Transdermal Patches (I-V)

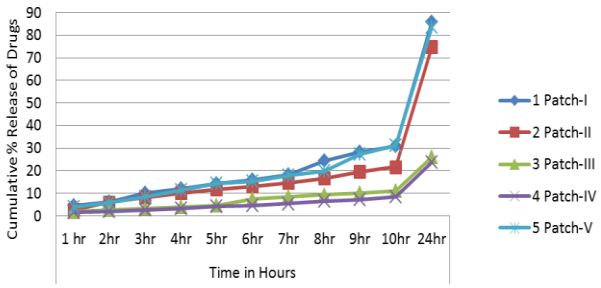


Figure 2. Skin irritation study of Patch-I (7th Day)

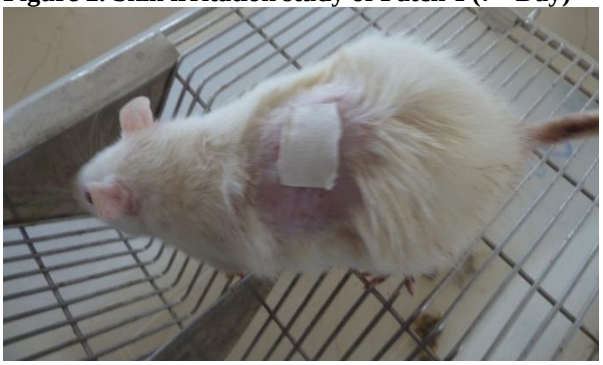


Figure 3. Skin irritation study of Patch- V (7th Day)

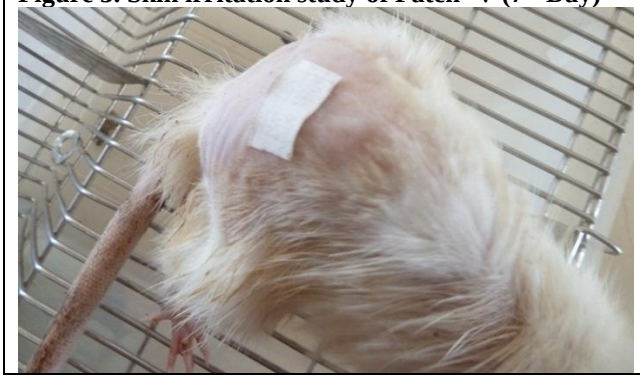
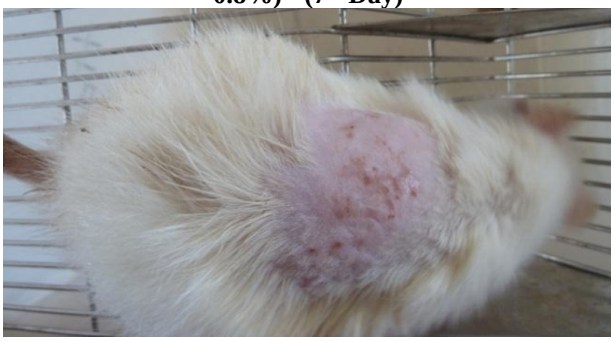


Figure 4. Skin irritation study of Standard (Formalin 0.8%) - (7th Day)



Weight variation

The results of weight variation are shown the table 2. There was no significant change observed in the average weight of patch-I to patch-V.

Thickness

The results of thickness for different Patchs are shown in the table 2. The high thickness of patch-IV was due to uneven distribution of polymer layer

and may be due to the low solubility of carbopol 940P in solvent system.

Folding endurance

The folding endurance values of all the patches were found satisfactory which indicates that the patches prepared using PEG-400 were having optimum flexibility and were not brittle. The results of folding endurance are shown in table 2.

Flatness

The results of flatness are shown in table 2. The results of flatness study shows that none of the formulations had the difference in the strip lengths before and after longitudinal cut, indicating 100% flatness and thus they could maintain a smooth surface when applied on to the skin.

Percentage moisture content & uptake

The results for % moisture content and uptake are shown in the table 3. The results revealed that the moisture uptake is found to increase with hydrophillic polymers. The results of the coded transdermal patches showed a marked difference in the moisture content .The patches-I and V showed higher moisture content and moisture uptake, which was due to the higher content of hydrophilic polymer HPMC K4M.The patches-II, II and IV showed less moisture content and uptake because of the blend of carbopol 940P. The lower moisture content in the formulation helps remain stable and become completely dried and brittle film. Low moisture uptake protects the material from microbial contamination and bulkiness.

Tensile strength and % elongation

The results for tensile strength and % elongation are shown in the table 3. The tensile strength of film was found to vary with the nature of the polymer. Among all the patches, patch-I and II shows higher tensile strength and % elongation. Tensile strength of transdermal patches usually increases due to PVP K-30.

Drug content

The results for drug content are shown in the table 3. There is no significant difference was observed in the drug content.

***In vitro* drug release studies**

The *in vitro* drug release studies carried out indicate the influence of polymers on the release of drugs. The cumulative percentage release of patch-I to patch-V over 24 hours were determined and summarized in table-4 and figure 1. Order of percentage drug release is as follows: Patch-I > Patch-V > Patch-II > Patch-III > Patch-IV

Skin irritation studies

The skin irritation study reveals that the formulated patches having excellent compatibility with skin. The prepared formulations were not produced any noticeable signs of erythema or edema on albino rats skin, indicating the skin compatibility of drug as well as polymer matrix. The results are summarized in table 5 & Fig. 2-4.

CONCLUSION

An attempt to develop transdermal therapeutic system for Dexibuprofen using polymers like HPMC K4M, MC, PVP K-30, Carbopol 940P was carried out for the purpose of attaining maximum bio availability by trespassing pre-systemic hepatic metabolism. The patches showed no significant variation in their average weight. The % moisture uptake was found to be high for the patches formulated with HPMC K4M: PVP K-30 (Patch-I) and HPMC K4M: MC (Patch-V). The reason behind the screen might be the higher proportions of hydrophilic polymer, HPMC K4M along with MC. All the patches showed uniform drug content. The Patch-I & V showed a better *in vitro* drug release profile across the cellulose membrane, when compared to other patches. This substantial increase may be attributed to the slow dissolving nature HPMC K4M, which might have facilitated more drug release from the matrix. Since the results of *in vitro* release studies were encouraging the Patch-I and Patch-V. The skin irritation studies using albino-rats revealed no signs of erythema or edema, which confirms the skin compatibility of the formulated transdermal patches (I-V). However stability studies, long term pharmacokinetic and pharmacodynamics studies should be under taken to establish the usefulness of these patches.

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