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FORMULATION AND EVALUATION OF TDDS OF DICLOFENAC SODIUM CONTAINING NATURAL PENETRATION ENHANCER

Pharmaceutical Science

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ABSTRACT

Transdermal drug delivery system is the system in which the delivery of the active ingredients of the drug occurs through the skin. Transdermal drug delivery system can improve the therapeutic efficacy and safety of the drugs because drug delivered through the skin at a predetermined and controlled rate. Skin is an effective medium from which absorption of the drug takes place and enters the circulatory system. The present investigation was aimed to prepare, characterize and evaluate transdermal matrix patches, Diclofenac Sodium for non-steroidal anti-inflammation and pain related disease. Based on results of various evaluation parameters like thickness, strength, elongation, better compatibility and stability the transdermal matrix patches was successfully designed and developed by trial and error method and evaluated for physicochemical parameters like thickness, weight variation, moister content, and drug content value. Transdermal matrix patched ware papered by using different concentration of ethyl cellulose. And it was concluded that the concentration of polymer increase the thickness of patches weight uniformity and folding endurance increase.

KEYWORDS

NSAID- Non-Steroidal Anti-Inflammation Disease, TDDS- Transdermal drug delivery system , PVP- Poly vinyl pyrrolidone, HPMC- Hydroxypropyl Methylcellulose.

INTRODUCTION

NSAID (Non-steroidal anti-inflammatory drugs) are mostly used for the preparation of transdermal patches for the treatment of inflammation or pain[1]. The NSAID patches are safer and convenient than its oral form. Patient with rheumatism received different NSAID tablets. The side effects like stomach bleeding, increased acidity, ulcers are avoided by using transdermal patches of NSAID. The analgesic patch of NSAID may be used on the site of bruise, sprain or strain[2]. These patch when applied topically in the form of transdermal patch, without reaching higher plasma drug concentrations the drug penetrate the skin, subcutaneous fatty tissue, and muscle in amounts sufficient to exert local therapeutic effects. Hence NSAIDs offer the advantage of local, enhanced drug delivery to affected tissues with a reduced incidence of systemic adverse events[3]. In Rheumatoid Arthritis patients are advised to take the NSAIDs for prolong period but the side effects related to systemic toxicity and GIT irritation are the main drawbacks of NSAIDs drugs. Diclofenac sodium is non-steroidal anti-inflammatory agent, widely used in musculoskeletal disorders, arthritis, toothache, etc., for symptomatic relief of pain and inflammation. Diclofenac sodium is reportedly used for topical applications[4-6]. The drug undergoes substantial hepatic first-pass metabolism and only about 50% of administered dose reaches systemic circulation. In Rheumatoid Arthritis patients are advised to take the NSAIDs.

MATERIALS AND METHODS

Materials

Diclofenac sodium was procured sample from Mylan Laboratories Limited Hyderabad, India, Hydroxypropyl methyl cellulose and Ethyl cellulose S.D. Fine Chemicals, Mumbai. Methanol, Chloroform and ethanol S.D. Fine Chemicals, Mumbai, were of analytical reagent grade. Oleic acid, Eucalyptus oil, Tea Tree oil& clove oil were procured from Gardens of Aroma Greater Noida, 201308, U.P.

Methods

Hydroxypropyl methyl cellulose and Ethyl cellulose was used for the formulation of Transdermal Patch Oleic acid is widely used in the solution phase synthesis of nanoparticles, functioning as a kinetic knob to control the size and morphology of nanoparticles[7-8]. Poly vinyl pyrrolidone was used as a plasticizer. Tea tree oil may be a good alternative antioxidant. Inherent antioxidants, Tea tree oil and Eucalyptus globulus oil is used as permeation enhancer[9-10]. The polymer was dissolved in chloroform: methanol (1:5) solvent. The drug was dispersed uniformly in the viscous solution with continuous stirring. The resulting mass was poured into in a Petri dish covered with inverted funnel. The Petri dish was left undisturbed at room temperature for one day[11]. The patch was obtained intact by slowly lifting from the Petri dish and transdermal patches were cut into radius of 2×2 cm^3.

Preparations Of Transdermal Patches

The transdermal patches of composition listed in **Table 1** were prepared by solution casting technique employing a glass substrate (Bangles wrapped with aluminium foil). Membrane type transdermal systems with containing 10 mg Diclofenac Sodium prepared by employing various proportions of $HPMCK_{15}M$, $PVPK_{30,}$ and Ethyl Cellulose[12]. The polymers was accurately weight and dissolved in a suitable solvent mixed until clear solution formed with magnetic stirrer then added drugs and placed for 30 mint in ultra sonicator bath machine (Elmasonic S150) for complete dissolution after that this sonicated solution mixed with PEG400 as a plasticizer[13]. The polymer solution was poured into bangles placed in a suitable level, hard rigid surface and patches were dried at a room temperature in a dust free environment for 24 hrs[14]. An inverted funnel was covered over the bangles to avoid fast evaporation of the solvent. Patches of 3.14 cm^2 were prepared by cutting and packed in an aluminum foil and kept in a desiccator.

Table 1: Composition of Transdermal patches

Formula-tion	Drug (mg)	HPMCK 15M (mg)	PVPK30 (mg)	EC (mg)	PEG-400* (ml)	Solvent (M:DCM) (1:1) (ml)	Natural Penetration Enhancer
Code							
F1	10	50	250	100	0.2	4	-
F2	10	50	250	100	0.2	4	2:04 (oleic acid &Eucalyptus oil)
F3	10	50	250	100	0.2	4	2:04 (oleic acid &Tea Tree oil)
F4	10	50	250	100	0.2	4	2:4 (oleic
F5	10	50	250	100	0.2	4	2:02:02

							(oleic acid, Eucalyptus oil & clove oil)
F6	10	50	250	100	0.2	4	2:2:2 (oleic acid, Eucalyptus oil & Tea Tree oil)
F7	10	50	250	100	0.2	4	2:2:2 (oleic acid, Tea Tree oil& clove oil)

Evaluation Of Transdermal Patches[15-20]

Thickness of patches

The thickness of Patches were measured by digital Vernier Calipers with least count 0.001mm at three different sites average of three reading was taken with standard deviation.

Weight Variation

The three disks of 3.14 cm^2 were cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch-to-batch variation.

Drug Content

Accurately weighed patches were individually dissolved in minimum quantity of methanol and made volume up to 100 ml with PBS pH 7.4 solutions; 10 ml was transferred to flask and made volume 100 ml. The absorbance was recorded. The blank solution was made in the same manner except the patches without drug were used.

Percentage Moisture Content

The films were weighed & placed in desiccators containing calcium chloride at 40^0c in a dryer for at least 24 hrs or more until it gives a constant weight. The %of moisture content was the difference between constant weigh taken and the initial weight and as reported with percentage by weight moisture content.

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage Moisture Absorption/ Uptake

The films of which the size 3.14cm^2 were put in a desiccators with silica gel for 24 hrs and weighed the patches were transferred to another desiccators containing saturated solution of KCL (84%RH) after equilibrium was attained. Patches were taken out and weighed. Moisture uptake was calculated with following formula:

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Swelling Index

The patches of 3.14 cm^2 were weighed and added into Petri dish whichcontains10mldoubledistilledwaterandwerepermeatedtoabsorb moisture at a fix time interval check the increase weight of the patches. Continue this process till same weight observed until weight remaining the same over a period of time. Swelling index (%S) was determined by applying the formula.

S (percentage) = Wt – Wo / Wo X 100
Where, S percent swelling, Wt patch weight at time t.
Wo patch weight at time zero.

Folding Endurance

This was obtained by constantly folding one patch at the same place without breaking gave the value of folding endurance. This test performed to check folding ability of transdermal patches also indicate brittleness of patches, more brittle patch when folding endurance value.

Percentage Elongation

A film strip (4 x 1cm) was cut on a glass plate with a sharp blade. The % elongation break is to be determined by observing the length just before the breaking point with formula by pointer on the graph paper.
% Elongation = [Final length – Initial length] * 100/Initial length

Tensile Strength

The tensile strength of the patches was found by the apparatus and the design of instrument such that, it had done wooden frame that horizontally placed having fixed scale. On the top of frame two clips were attached to hold patches that under study. From two clips one clips fixed & other moved. Instrument also has pulley to hold weight a patch, weight applied to one end of pulley and other end attached to the fixed clip. During the test wooden platform not dislocate from the original place so platform was fixed carefully to avoid dislocation. Three patches were cut for study having 3.14 cm^2 sizes. Thickness and width of patches were noted at three sizes and calculated average value. Rate of stress changes was maintained constant with the addition of 0.5g per 2 minutes. The elongation was observed and the total weights taken were used for calculation.

Formula for tensile strength:
Tensile strength= F/a.b (1+L/l)

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***In-vitro* permeation Studies**

Franz diffusion cell (fabricated in our Lab.) with a diameter 3.7cm was used in in-vitro release studies. A glass tube with both end open, 10cm height and 3.7cm outer diameter was used as a permeation cell[21]. A transdermal patch sample was accurately placed on a semipermeable cellophane membrane to occupy a circle of 3.7cm diameter. The loaded membrane was stretched over the lower open end of a glass tube of 3.7cm diameter and made water tight by rubber band. The tube (donor compartment) was immersed in a beaker containing 100 ml of phosphate buffer pH 6.8 (receptor compartment) .The cell was immersed to a depth of 1 cm below the surface of buffer. The system temperature was maintained at 37°±1° and speed was maintained at 30 rpm throughout the experiment by magnetic stirrer. The samples 3 ml were withdrawn at different time intervals and analyzed without dilution or filtration for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Stability Studies

As per ICH Guidelines of Accelerated stability studies were performed at the different storage condition 25°C±2^0c temp., 60%±5% RH and 40°C±2^0c temperature, 75%±5% RH, for 90 days on optimized formulation batches (F6).The parameters studied for stability studies are thickness, drug content, moisture content and uptake, weight variation, folding endurance, Tensile strength, % elongation and swelling index[22].

RESULTS AND DISCUSSION

Preformulation Studies

The Diclofenac Sodium sample shows white to slightly yellowish crystalline powder.

Melting Point

The Diclofenac Sodium M.P. was observed 282 °C

Solubility

Solubility profile of drug is freely soluble in methanol, soluble in ethanol, and acetone and slightly soluble in ethanol, and sparingly soluble in water. Diclofenac sodium is poorly soluble, highly permeable (Class II) drugs[23]; the drug was shown to have pH dependent solubility. With increase in pH, increase in the protonation (ionization) of the carboxylic acid moiety resulted in abrupt increase in solubility of drug in alkaline pH. Further, increase in pH to 8.0 was not found to increase solubility[24]. Diclofenac Sodium has been shown as a practically insoluble drug at pH 1.2 and slightly soluble at pH 7.2

Standard curve of Diclofenac Sodium

The standard curve for Diclofenac Sodium in PBS pH 7.2 was made. The method followed Beer's law limit in the proportions range of 2-12 mcg/ml at 276 nm with a R^2 value of 0.997.

Table 2: Standard Curve Of Diclofenac Sodium.

Sr. No	Concentration (µg /ml)	Absorbance at 276 nm pH 7.4
0	0	0

1	2	0.026
2	4	0.068
3	6	0.106
4	8	0.148
5	10	0.186
6	12	0.221

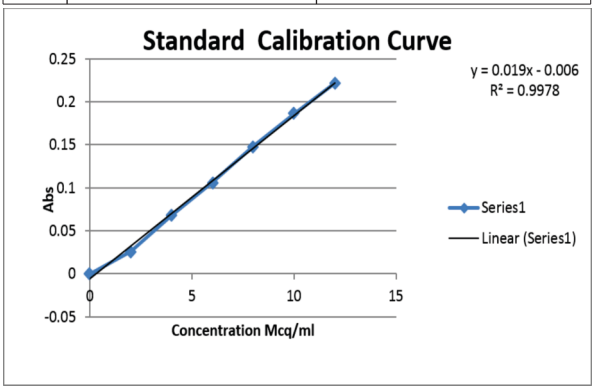

Figure 1: Standard curve of Diclofenac Sodium using Phosphate buffer 7.4 pH at 276 nm

Fourier Transform-Infrared Spectroscopy Studies (FT-IR) Studies:

Drug polymer compatibility studies were carried out using FT-IR spectroscopy to establish any possible interaction of Diclofenac Sodium drug with the excipients and natural permeation enhancers used in the formulation[25]. The FT-IR spectra results indicated that mixture of pure drug and excipients has no major change in the position of peaks. This shows that there is no possible interaction between drug and excipients.

Evaluation Of Transdermal Patches

FTIR Studies for Transdermal Patches

The FTIR spectra are recorded over the wave number range of 4000–400 cm^{-1}. The Diclofenac Sodium drug showed different peaks which confirms the purity of the Diclofenac Sodium drug. The same peaks are also found in the FT-IR spectra of the formulations mixtures (**Diclofenac Sodium + HPMC+ PVP+ EC+ PEG-400**) and (**Diclofenac Sodium + HPMC+ PVP+ EC+ PEG-400+ Eucalyptus Oil, Oleic Acid And Tea Tree Oil**), showing that no drug– polymer interaction occurred. In FT–IR studies the characteristic peak due to pure Diclofenac Sodium has appeared in the spectra of formulations mixtures.

Therefore, there were no alterations and no interactions observed between polymers, additives and drug in combination. All the characteristic peaks of Diclofenac Sodium are present FTIR spectra in combination thus indicating compatibility between drug and polymers and finally confirm that there was no chemical modification of the drug has been taken place.

Table 3: FTIR of Diclofenac Sodium

S.No.	Wave number (cm-1)	Due to…	Functional Group	Peak Assigned
1	3700-2500	Alcohol of carboxylic acid	O-H str.	3355
2	3000-2800	Alkane group(-CH3)	C-H str.	3054
3	1760	Carbonyl group	C=O str.	1741
4	1600	Carbon- carbon double bond	C = C str.	1647
5	1450	Ether	CH3- O str.	1410

Physicochemical Evaluation

Tables shows the physicochemical evaluation like the Thickness, Folding endurance, Percentage moisture absorbed, Percentage moisture lost, Drug content uniformity[26].

Table 4: Physicochemical Evaluation data of Diclofenac Sodium Transdermal Patches

Formulation Code	Thickness (mm)	Weight variation (mg)	% Drug Content Diclofenac Sodium	Folding endurance	Tensile strength Kg/mm2
F1	0.31±0.09	0.159±0.01	98.15±2.02	58±02.04	3.21±0.81
F2	0.30±0.02	0.151±0.005	98.4±2.42	57.7±12.0	2.89±0.70
F3	0.32±0.004	0.150±0.021	97.42±2.17	58±08.20	3.12±0.70
F4	0.31±0.09	0.158±0.011	98.73±1.43	59±14.13	3.30±1.70
F6	0.32±0.29	0.154±0.017	98.34±2.02	58±22.03	3.34 ±1.80
F6	0.31±0.013	0.156±0.014	98.91±1.42	58±11.42	3.33±1.83
F7	0.32±0.012	0.157±0.015	98.33±2. 02	59±59.41	3.34 ±1.76

Permeation studies and Permeation Kinetics

The drug permeation from the Patches is depends on the polymer type as well used concentration. In- Vitro (permeation) studies were performed with Franz cell in Phosphate Buffer Saline pH 7.4. In drug Permeation study the formulation F1 without containing permeation enhancer shows 40.23% at 12 hrs and 52.41 at 24 hrs while F6 containing as the standard permeation enhancer shows maximum drug permeation 88.24 % at 12 hrs and 98.12 at 24 hrs. The drug permeation data of F6 was plotted for Zero order, First order, Higuchi model and Korsmeyer-Peppas model to evaluate the permeation pattern of the dosage form[27]. From these plots, kinetic values of the drug permeation were determined. Drug released from the matrix devices by diffusion studied with first order Model and result suggested that the drug permeation follow first order model.

Table 5: Physicochemical Evaluation Data Of Diclofenac Sodium Transdermal Patches

Formulation Code	% Elongation	% Moisture Content	% Moisture uptake	Swelling index
F1	33.23±2.51	2.68±0.35	4.37±4.03	24.31±1.28
F2	33.10±2.12	2.53±0.77	4.25±2.7	23.82±0.52
F3	34.65±2.61	2.79±1.29	5.24±1.22	23.89±1.12
F4	35.71±4.12	2.81±1.82	5.16±0.85	24.71±0.74
F5	35.94±4.71	2.55±2.78	5.15±1.25	24.49±0.15
F6	35.02±4.19	2.54±0.98	5.14±1.06	24.50±1.37
F7	32.58±4.17	3.57±0.97	4.49±1.05	24.21±1.26

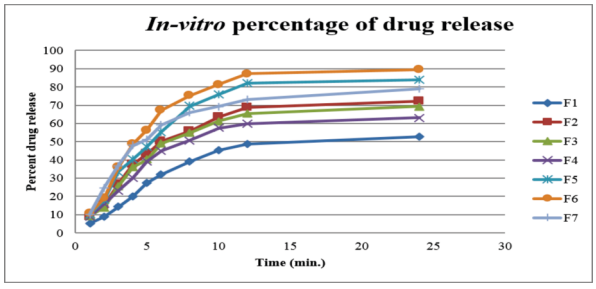

Figure 2: In-vitro percentage of drug release

Drug Release Kinetic Modeling Of Optimized Formula

On comparison of kinetic modeling and release profile data it was evident that Transdermal Patch containing Diclofenac Sodium was found to release the drug in accordance to Hixson rate order kinetics, the regression coefficient was not found to be exactly near to 1, which could be due to influence of some other factors.(fig.5.8-5.12 7.2.5.1-7.2.5.)

Table 6: R2 Value Of Optimized Formulation Tf6

Model Name	Zero order	Fist order	Higuchi model	Hixson	Cross peppas	Best fit model
R2 value of F6 for Diclofenac Sodium	0.9924	0.979	0.9092	0.9884	0.959	First order Hixson model

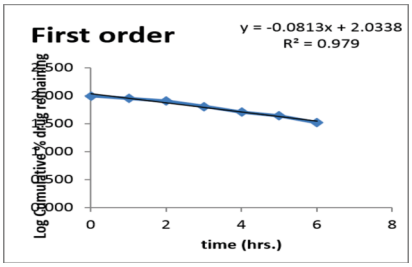

Figure 3: First order Kinetic Model for Diclofenac Sodium Trasdermal Patch formulation F-6

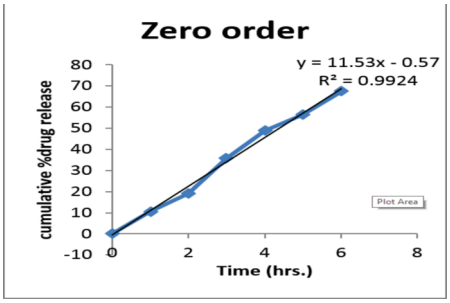

Figure 4: Zero order Kinetic Model for Diclofenac Sodium TrasdermalPatch formulation F-6

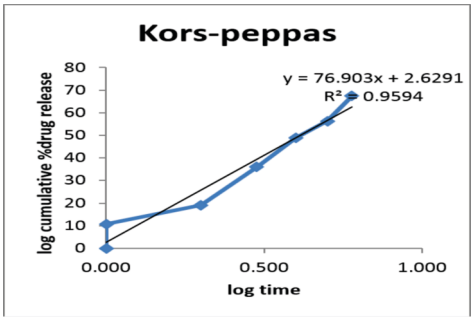

Figure 5: Korsmeyerpeppas Model for Diclofenac Sodium Trasdermal Patch formulation F-6,

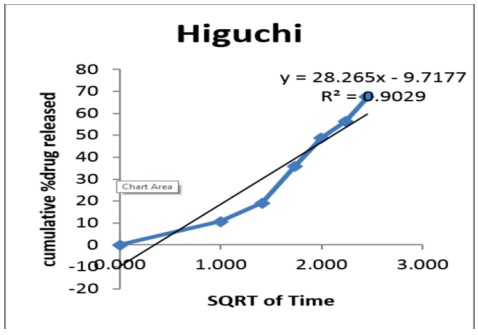

Figure 6: Higuchi Model for Diclofenac Sodium Trasdermal Patch formulation F-6

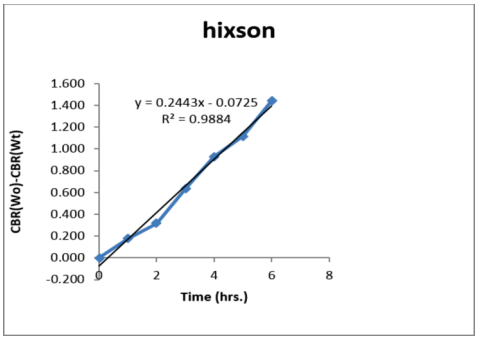

Figure 7: Hixson Crowell Model for Diclofenac Sodium Transdermal Patch formulation F-6

Stability Study

Stability is the essential factor for quality, safety and efficacy of product. stability studies as per ICH guidelines and observed for all evaluation parameters at a temperature of 25^{0}C and 60% RH, 40^{0}C and 75% RH, at an interval of three month. There were no physical changes in flexibility and physicochemical evaluation parameter was slightly changed (Table)

Table 7: Stability Study of Diclofenac Sodium TDDS batch F6

S. No	Evaluation Parameter	At 0 day	After 90 days
1	Thickness (mm)	0.31±0.29	0.29 ± 0.26
2	Weight variation	0.153±0.017	0.164 ± 0.021
3	% Drug Content of Diclofenac Sodium	98.71±1.43	98±14.13
4	Folding endurance	57±22.03	56 ± 31.13
5	Tensile Strength Kg/mm2	3.35 ±1.84	3.22±1.50
6	% Elongation	35.71±4.12	34.19 ± 4.12
7	% Moisture content	2.81±1.82	3.1 ± 0.94
8	% Moisture uptake	5.16±0.85	5.18 ± 3.03
9	Swelling index	24.51±0.74	23.40 ± 0.71

CONCLUSION

In the present study, an attempt was made to prepare, characterize and evaluate of transdermal matrix patches of Diclofenac Sodium for inflammation and pain related disease. Based on results of various evaluation parameters like thickness, strength, elongation, better compatibility and stability the transdermal matrix patches was successfully designed and developed by trial and error method. Formulations were prepared by employing combination of HPMCK$_{15}$M, PVPK$_{30,}$ PEG-400 and EC among penetration enhancer and patches were evaluated for uniformity of thickness, weight-variation test, folding-endurance, tensile strength, % elongation, % flatness, % moistures absorption, Moistures vapor transmittance rate, assay done. Cellophane membrane employed for the diffusion study.

The Tensile-strength of film found to be in range of 2.89±0.80 to 3.35 ±1.84 Kg/mm^2. Flatness of all prepared patches was found to be 100%. Folding-Endurance of patch found to be in range of 57±22.03 to 59±14.13. The drug contents found in between 97.41±2.17 to 98.5±2.42. The % moisture absorption for all batches found to be in range of 2.53±0.77 to 3.53±0.98 %. The % moisture uptake for all batches found to be in range of 4.25±2.7 to 5.25±1.25 %. % Elongation for all formulation was in the range of 32.98±4.18 to 36.94±4.71 %. The In vitro diffusion studies were performed in phosphate-buffer pH-7.4 for 24hours. The batch F6 was optimized batch of Diclofenac Sodium transdermal patches prepared by using HPMCK$_{15}$M, PVPK$_{30,}$ PEG-400 and EC with natural permeation enhancer oleic acid, eucalyptus oil and tea tree oil showed good physical properties and ideal release kinetics.

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