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Research Article

Formulation and Evaluation of Transdermal Patch Containing Natural Penetration Enhancer

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Abstract

The purpose of the work was to formulate and evaluate the Indomethacin e transdermal patches with natural permeation enhancer for the controlled delivery of the drug in the body. Patches were formulated using various ratios of polymer $HPMCK_{15}M$, ($PVPK_{30}$) Polyvinyl Pyrrolidone and Ethyl Cellulose. Transdermal patches were formulated by solvent evaporation method. Transdermal patches were evaluated for various parameters like thickness, folding endurance, percentage moisture loss, percentage moisture absorption, drug content uniformity, stability studies, *in vitro* skin permeation and skin irritation test. All formulations possess excellent physicochemical properties and exhibited negligible skin irritation with good physical stability. Permeation study was performed by using modified Franz diffusion cells. On the basis of drug release and physicochemical values, formulation F7 with natural permeation enhancer was shows higher percentage of drug release at 24 hours. Release kinetics studies revealed that the drug release from formulations followed Higuchi kinetics

.**Keywords:** Indomethacin, ,Transdermal patches, Polymer, $HPMCK_{15}M$, *In vitro*

Introduction : Transdermal route is, therefore, a better alternative to achieve constant plasma levels for prolonged periods of time, which additionally could be advantageous because of less frequent dosing regimens. To provide continuous drug infusion through an intact skin, various transdermal systems have been designed for topical application and it control the delivery of drug and its permeation via the skin tissue. Historically, developments related to TDDS have been incremental, concentrating on overcoming issue related with the skin barrier properties, minimizing skin irritation and improving the outlook related with passive patch systems. TDDS defined as self-contained, discrete dosage form applied to the unharmed skin then it deliver the drug, via skin at controlled manner in the systemic circulation. Transdermal drug delivery via the skin provides a suitable route of administration for a various clinical indications.

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A pharmaceutical scientist focuses the development of transdermal drug delivery over the last 25 years. The skin offers a large and easily penetrable surface for drug delivery. Transdermal routes, from that of other routes are quite non-invasive, like simple adhesion of a "Patch" similar as that of application of a Band-Aid. A transdermal drug delivery systems transfer a precise dose of drug through the skin and into systemic circulation.
Transdermal delivery is important because it is a non-invasive procedure for drug delivery. Further, problem of drug degradation by digestive enzymes after oral administration, gastric irritation and discomfort associated with parenteral drug administration can be avoided. Transdermal drug delivery is the non-invasive delivery of medications from the surface of skin-the largest and most accessible organ of human body- through its layers, to the circulatory system. TDDS offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. .[4-5]

Materials and Methods

Preparation of Standard Curve [7]

Stock solution: Accurately weighted 100 mg of indomethacin was dissolved separately in 10 ml of methanol in 100 ml of volumetric flasks and volume was made up to 100ml with pH 7.4 phosphate buffer to get a solution 1000µg/ml concentration.

Standard solution: From primary stock solution of 10 ml was pipette out in a 100 ml of volumetric flask and volume was made up to the mark with pH 7.4 buffer to get a concentration of 100 µg/ml. Aliquot of standard drug solution ranging from 1ml to 8ml were transferred in to 10ml volumetric flask and were diluted up to the mark with pH 7.4 phosphate buffer. Thus the final concentration ranges from 10-60 µg/ml. Absorbance of each solution was measured at 320 nm against pH 7.4 phosphate buffer as a blank. A plot of concentrations of drug versus absorbance was plotted.

FT–IR spectral analysis

The development of a successful formulation depends only on a suitable selection of excipients. Hence the physical state of the drug indomethacin and the polymers, EC, $HPMCK_{15}M$, $PVPK_{30}$, PEG-400 and Methanol individually are studied by FTIR (Fourier transform

infrared spectroscopy) to know the drug–polymer compatibility. The physicochemical compatibility of the drugs and the polymer was obtained by FTIR studies.

Preparations of transdermal patches

The transdermal patches of composition listed in Table no.2 were prepared by solution casting technique employing a glass substrate (Bangles wrapped with aluminium foil). Membrane type transdermal systems with containing 75 mg Indomethacin prepared by employing various proportions of $HPMCK_{15}M$, $PVPK_{30}$, and Ethyl Cellulose. 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 .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. 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.

Evaluation of Transdermal Patches

Thickness of patches [9]

The thickness of Patches was 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 [9]

The three disks of 3.14 cm^2 was 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 ethanol 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.[9]

Table 1: Formulation of transdermal patches

Formulation Code	Drug (mg)	$HPMCK_{15}M$ (mg)	$PVPK_{30}$ (mg)	EC (mg)	PEG-400* (ml)	Solvent (M:DCM) (1:1) (ml)	DMSO(ml)
F1	75	50	250	100	0.2	4	-
F2	75	50	250	100	0.2	4	20
F3	75	50	250	100	0.2	4	-
F4	75	50	250	100	0.2	4	-
F5	75	50	250	100	0.2	4	-
F6	75	50	250	100	0.2	4	-
F7	75	50	250	100	0.2	4	-

*HPMC: Hydroxypropyl methyl cellulose, PVP: Polyvinyl pyrolidone, PEG : Polyethylene glycol, DMSO: Dimethyl sulphoxide, *M: Methanol *DCM: Dichloromethane*

Percentage Moisture content [10]

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 weight taken and the initial weight and as reported with percentage by weight moisture content.

Percentage Moisture absorption/uptake [10]

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.

Swelling index[11]

The patches of 3.14 cm² were weighed and added into Petri dish which contains 10 ml double distilled water and were permeated to absorb 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.

***In-vitro* permeation studies** [13-18]

Franz diffusion cell (fabricated in our Lab.) with a diameter 3.7 cm was used in in-vitro release studies. A glass tube with both end open, 10 cm height and 3.7 cm outer diameter was used as a permeation cell. A transdermal patch sample was accurately placed on a semipermeable cellophane membrane to occupy a circle of 3.7 cm diameter. The loaded membrane was stretched over the lower open end of a glass tube of 3.7 cm 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[14-18]

Stability studies were subjected to a stability testing for six months as per ICH norms at a temperature and RH of 40°C ± 2°C/75% RH ± 5% RH respectively, for 90 days

Results and discussion

Standard curve of Indomethacin

Table no.2 and Fig-1 shows the standard curve for Indomethacin in phosphate buffer pH 7.4. The method obeyed Beer's law limit in the concentration range of 2-14 mcg/ml at 270 nm with a regression value of 0.996

Table no2: Standard curve of Indomethacin.

S.No	Concentration (Mcg/ml)	Absorbance at 320 nm
0	0	0
1	2	0.027
2	4	0.069
3	6	0.104
4	8	0.146
5	10	0.183
6	12	0.21
7	14	0.241

FTIR Studies for Transdermal Patches

Fourier transformed infrared (FTIR) spectra technique have been used here to study the physical and chemical interaction between extracts and excipients used in formulation. From the study, it has been observed that there is no changes in these main peaks in IR spectra of mixture of Indomethacin, polymers and permeation enhancers used in formulation which shown there were no physical and chemical interaction. The peaks obtained in the spectra's of formulation correlated with the peaks of Indomethacin drug. This indicates that the extract was compatible with the formulation.

Formulations of Transdermal Patches :

Seven formulations of Indomethacin tansdermal patches compose with different polymers HPMCK_{15}M, PVPK_{30}, Ethyl cellulose. Methanol and Dichloromethane were used as a casting solvent. PEG400 used to give plasticity to

patches while Dimethyl sulphoxide is used to enhance penetration of drug through transdermal systems. The polymeric 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. an inverted funnel was covered over the bangles to avoid fast evaporation of the solvent. Patches of 3.14 cm2 were prepared by cutting and packed in an systems were smooth, thin and flexible. The preparation method of patches was found satisfactory.

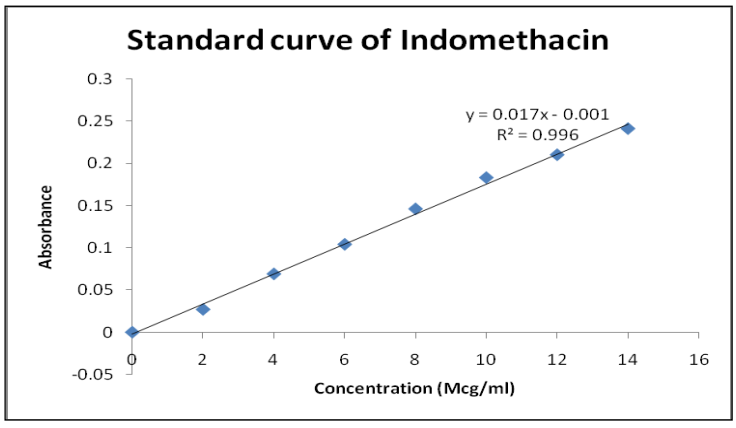
Evaluation of Transdermal patches

Table 3 and 4 shows the physicochemical evaluation like the Thickness, Folding endurance, Percentage moisture absorbed, Percentage moisture lost, Drug content uniformity.

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 F2 containing DMSO as the standard permeation enhancer shows 73.61% at 12 hrs and 76.77 at 24 hrs while F7 shows maximum drug permeation 66.24 % at 12 hrs and 75.87 at 24 hrs. The drug permeation data of F7 was plotted for Zero order, First order, Table 5)

Fig.1: Standard curve of Indomethacin



Stability Study

Stability is the essential factor for quality, safety and efficacy of product. The drug product is with insufficient stability result in altering of their physical as well as chemical characteristics. All formulations were subjected for stability studies and observed for all evaluation parameters at a temperature of40^{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-6)

Fig 2 *In-vitro* Drug Permeation Indomethacin TDDS

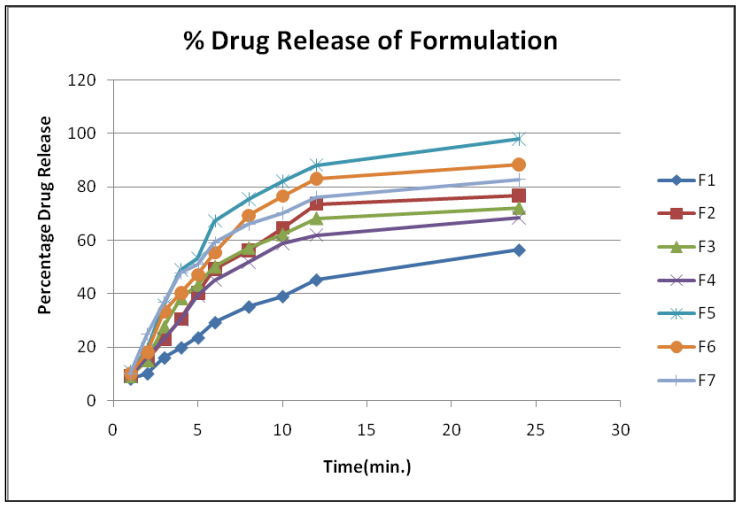


Table 3: Physicochemical Evaluation data of Transdermal Patches

Formulation Code	**Thickness (mm)**	**Weight variation (mg)**	**% Drug Content**	**Folding endurance**	**Tensile strength Kg/mm²**
			Indomethacin		
F1	0.30±0.09	0.159±0.01	98.12±2.02	58±02.04	3.21±0.81
F2	0.29±0.02	0.151±0.005	9.85±2.42	57.7±12.0	2.89±0.80
F3	0.31±0.004	0.150±0.021	97.41±2.17	58±08.20	3.12±0.70
F5	0.32±0.09	0.159±0.011	98.71±1.43	59±14.13	3.31±1.80
F5	0.31±0.29	0.153±0.017	98.12±2.02	57±22.03	3.35 ±1.84
F6	0.32±0.003	0.158±0.014	97.91±1.42	57±11.42	2.94±1.84
F7	0.31±0.013	0.157±0.015	98.36±2.02	58±59.41	3.24 ±1.78

Table: 1 (b) Composition of Natural penetration enhancer in Transdermal patches

Formulation Code	**Natural Penetration Enhancer in parentage**			
	Oleic acid	**Camphor**	**Menthol**	**Clove oil**
F1	-	-	-	-
F2	2	4		
F3	2		4	
F4	2			4
F5	2	2	2	
F6	2	2		2
F7	2		2	2

Table 4 .Physicochemical Evaluation data of Transdermal Patches of Indomethacin

Formulation Code	% Elongation	% Moisture Content	% Moisture uptake	Swelling index
F1	33.23±2.51	2.68±0.35	4.37±4.03	25.31±1.28
F2	33.10±2.12	2.53±0.77	4.25±2.7	24.71±0.52
F3	34.65±2.61	2.79±1.29	5.24±1.22	24.49±1.12
F5	35.71±4.12	2.81±1.82	5.16±0.85	24.51±0.74
F5	36.94±4.71	3.35±2.78	5.25±1.25	24.12±0.15
F6	3502±4.19	3.53±0.98	4.35±1.06	25.10±1.37
F7	32.98±4.18	3.27±0.97	4.49±1.05	24.22±1.26

Table 5 *In-vitro* Drug Permeation of Indomethacin Kinetics

Time (hrs)	F1	F2	F3	F4	F5	F6	F7
1	5.08	9.03	9.1	9.03	10.71	10.21	10.12
2	9.03	14.99	15.12	15.89	19.14	18.22	24.89
3	11.99	22.81	27.65	23.07	35.85	33.45	36.86
4	17.81	30.52	38.26	30.24	48.86	40.36	47.86
5	20.52	40.24	43.28	39.28	53.28	47.24	51.12
6	24.23	49.23	50.12	45.02	67.32	55.44	59.12
8	29.12	56.21	57.12	51.76	75.42	69.46	66.12
10	34.03	64.56	62.21	58.68	82.21	76.71	70.21
12	40.23	73.61	68.24	61.87	88.24	83.24	76.24
24	52.41	76.77	75.12	68.43	98.12	88.51	82.87

Table 6 Stability Study of TDDS of Indomethacin

Formulation Code	% Drug Content	
	At 0 day	After 90 days
F1	98.12±2.02	98.11 ± 1.25
F2	98.5±2.42	98.2±2.42
F3	97.41±2.17	96.94±2.17
F5	98.71±1.43	98±14.13
F5	98.12±2.02	97±22.03
F6	97.91±1.42	97±11.22
F7	98.36±2.02	98.21±1.20

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