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Formulation and Evaluation of Indomethacin Transdermal Patch Containing Natural Penetration Enhancer

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Research Article

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 F5 with natural permeation enhancer was shows higher percentage of drug release at 24 hours.

Keyboard

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

Introduction

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.

Indometacin, also known as indomethacin, is a nonsteroidal anti-inflammatory drug (NSAID) commonly used as a prescription medication to reduce fever, pain, stiffness, and swelling from inflammation. It works by inhibiting the production of prostaglandins, endogenous signaling molecules known to cause these symptoms. It does this by inhibiting cyclooxygenase, an enzyme that catalyzes the production of prostaglandins.

Permeation enhancers are those substances which promote the absorption of drug through the skin temporarily by transiently enhancing the skin permeability. They are employed to transfer the delivery of drugs which are ionizable (Example: timolol maleate) and impermeable (Example: heparin); to maintain drug levels in blood, to provide higher dose of less potentially active drugs (Example: Oxymorphane), to deliver high molecular weight hormones and peptides and to lessen the lag time of transdermal drug delivery system. [1-7]

Material and Methods

Preparation of Standard Curve

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.

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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

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

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.

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

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

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. Moisture uptake was calculated with following formula

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

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.

Folding endurance[12]

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 [12]

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 [13]

The tensile strength of the patches was found by the apparatus and the design of instrument such that, it had one 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 breadth 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)

Where,
F is the force required to break; 'a' is width of film; 'b' thickness of film; L is length of the film; l is an elongation of film at break point

***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.

Result 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

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 camphor, oleic acid, menthol and clove oil 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 F1 without containing permeation enhancer shows 40.23% at 12 hrs and 52.41 at 24 hrs while F5 containing as the standard permeation enhancer shows maximum drug permeation 88.24 % at 12 hrs and 98.12 at 24 hrs.

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)

Conclusion

TDDS are the ideal delivery system for drug that undergo hepatic first pass metabolism. Based on results of various evaluation parameters like thickness, strength, elongation, better compatibility and stability the transdermal matrix patches containing drug was successfully designed and developed by trial and error method. Formulations were prepared by employing combination of HPMCK15M, PVPK30, and EC in various ratios. From the research, various conclusions were drawn.

- From the evaluation results it was conclude that F5 show highest release at 12 hrs. with suitable polymer ratio and penetration enhancer.
- From the kinetic study it was observed that Higuchi kinetics model most suitable kinetic model for drug release from all patches.
- Stability study performed on optimized formulation. No major changes showed in the parameters during study period, thus it could be concluded that formulation was stable.

Reference

1. Aggarwal G, Dhawan S, Hari Kumar S. Formulation, in vitro and in vivo evaluation of transdermal patches containing risperidone. Drug Dev Ind Pharm. 2013;39:39–50.
2. Dua K, Penetration enhancer for Transdermal drug delivery system; A tale of the under skin travelers. Advances in natural and applied sciences2009; 1:95-101.
3. Kandavilli S, Nair V, Panchagnula R. "Polymers in transdermal drug delivery systems, Pharmaceutical Technology" 2002, p62-78. Available from: *www.pharmtech.com*. Accessed on 15 Jan, 2008.
4. Ratan Mehta. "Topical and transdermal drug delivery": What a Pharmacist Needs to Know. *ACEP;* 1-10.
5. Yie W Chein. Eds. Yie W. Chein-"Transdermal Drug Delivery Systems and Delivery Systems", 2nd ed: *MARCEL DEKKER, INC*; 1992 p301.
6. Roopa Pai S. and Kusum Devi V. "Lamivudine Liposomes for Transdermal Delivery Formulation, Characterization, Stability and In vitro *Evaluation*".*International Journal of Pharmaceutical Sciences and Nanotechnology* Volume 1,Issue 4,January-March 2009 p317 – 326.
7. Jaydatt k. Jadhav.1, S.A.sreenivas, formulation and in-vitro evaluation of indomethacin transdermal patches using polymers HPMC E5 and ethyl cellulose, International journal of pharmacy and pharmaceutical sciences, vol 4, suppl 1, 2012, 550-556
8. Kavitha K., More MR., Design and evaluation of transderrmal films of Lornoxicam Int. J. Pharma & Bio Sci, 2011, 2(2), 54-62
9. Patel DM., Kavitha K., Formulation & Evaluation aspects of transdermal drug delivery system, Int. J. Pharma Sci. Rev. Res. 2011, 6(2), 83-90
10. Suchika Sharma, Geeta Aggarwal, Sanju Dhawan. Design and evaluation of Olanzapine transdermal patches containing vegetable oils as permeation enhancers. Scho. Res. Lib. 2010; 2(6):84-98
11. Kooriyattil Naseera, C I Sajeeth, K Santhi. Formulation, Optimization and Evaluation of Matrix Type of Transdermal System of Simvastatin Using Permeation Enhancers. Int. J. Curr. Pharma. Res.2012; 4 (2):79-87
12. Gajanan Darwhekar, Dinesh Kumar Jain, Vinod Kumar Patidar, Formulation and Evaluation of transdermal drug delivery system of Clopidogrel Bisulphate, Asian Journal of Pharmacy and Life Science Vol.1(3),2011,269-278
13. Jadhav Jaydatt, Sreenivas SA. Formulation & *In-vitro* Evaluation of Drug Reservoir Transdermal Patches of Piroxicam Using Polymers HPMC E15, PVP K30 & Eudragit L100. Int. J. Pharm. 2013; 3 (5):67-80
14. Sankar V, Johnson DB, Sivanand V, Ravichandran V, Raghuraman S, Velrajan G, Design and evaluation of nifedipine transdermal patches.Indian J Pharm Sci. 2003; 65(5): 510-515
15. Costa P. Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci.13,123-133(2001)
16. Praveen M, Someswara Rao B, Kulkarni S.V., Chethan Surpur Basavaraj. Formulation and Evaluation of Tizanidine Hydrochloride Transdermal Patches Int. J. Drug. Pharma. Res. 2011; 2(2): 298-313

Table:1 Composition of Transdermal patches

Formulation Code	Drug (mg)	HPMC $K_{15}M$ (mg)	PVP K_{30} (mg)	EC (mg)	PEG-400* (ml)	Solvent (M:DCM) (1:1) (ml)	Natural Penetration Enhancer
F1	75	50	250	100	0.2	4	-
F2	75	50	250	100	0.2	4	2:4 (oleic acid & camphor)
F3	75	50	250	100	0.2	4	2:4 (oleic acid & Menthol)
F4	75	50	250	100	0.2	4	2:4

Table: 2 Composition of Natural penetration enhancer in Transdermal patch

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

							(oleic acid &clove oil)
F5	75	50	250	100	0.2	4	2:2:2(oleic acid, camphor & menthol)
F6	75	50	250	100	0.2	4	2:2:2(oleic acid, camphor & clove oil)
F7	75	50	250	100	0.2	4	2:2:2 (oleic acid, menthol& clove oil)

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Fig.1: Standard curve of Indomethacin

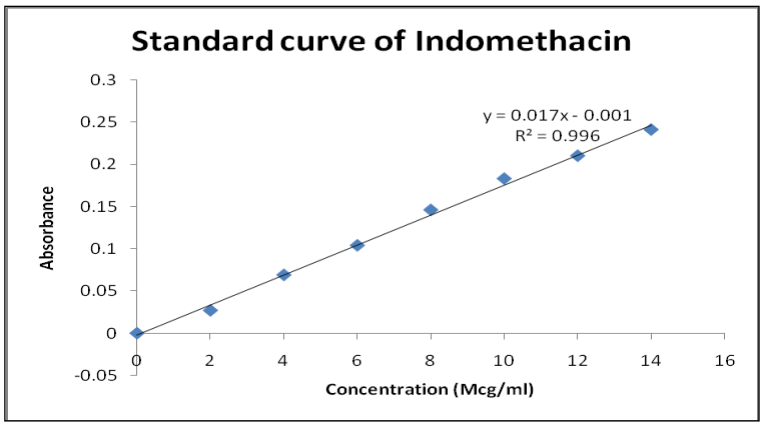

Table 3: Physicochemical Evaluation data of Transdermal Patches

Formulation Code	Thickness (mm)	Weight variation (mg)	% Drug Content Indomethacin	Folding endurance	Tensile strength Kg/mm^2
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	98.5±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
F4	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 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
F4	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	19.12	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**

Fig 2 In-vitro % drug release of Indomethacin TDDS with Permeation enhancer

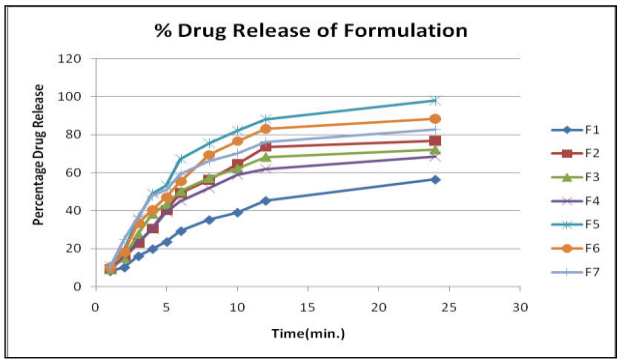

Table 6 Stability Study of TDDS of Indomethacin

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	98.34±2.02	98±22.03
F6	97.91±1.42	97±11.22
F7	98.36±2.02	98.21±1.20

Table no 2: 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