FORMULATION AND EVALUATION OF TDDS OF INDOMETHACIN CONTAINING NATURAL PENETRATION ENHANCER

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ABSTRACT

In the present study, an attempt was made to prepare, characterize and evaluate of transdermal matrix patches of Indomethacin 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 HPMCK15M, PVPK30, 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. There were no physical changes in flexibility and physicochemical evaluation parameter was slightly changed.

Keywords: *Indomethacin, TDDS, matrix patches, Penetration Enhancer,*

1. INTRODUTION

Present research work is to formulate, development and characterization of transdermal systems for Indomethacin with Natural permeation enhancer drug. The controlled release matrix tablets and matrix type transdermal patches with varying proportions of polymers were prepared, studied the drug and polymer interaction, better bioavailability, minimize the dose[1,2]. When the TDD patch apply on the skin, drugs penetrating in to skin into blood circulation by different skin pathways[3,4]. The drug(s) get systemic circulation by 1. Stratum corneum is transepidermal route or 2. An appendage is transappendageal route[,5]. Penetration of drug into stratum corneum there are two routes can possible i) Penetration occur by alternating the lipid layer and corneocytes as known as transcellular route ii) penetration occur as result of the convoluted pathway along the lipid layer also known as intercellular route[6]. Permeation promoters or enhancers are substances which are not having therapeutic activity but can move from therapeutic system into skin by sorption mechanism[7].

In this work, the Indomethacin drugs was chosen as a suitable drug candidate to explore its potentiality in being delivered Controlled drug delivery systems with Natural permeation enhancer which also give anti- inflammatory action. Rationale behind selecting Natural permeation enhancer in TDDS system to fulfill objective of topical delivery system that is enhanced delivery of active agents at deeper level of skin.

2. MATERIALS AND METHODS

2.1 Preformulation Study

Melting point: It was determined by melting point apparatus.

Solubility study: Preformulation solubility analysis was done, which include the selection of a suitable solvent, to dissolve the respective drug.In order to assess in-house solubility for the obtained drug sample, solubility measurements were performed according to the shake flask method. In brief, excess amount of indomethacin was added into eppendorf tubes to which 10 ml of aqueous buffer medium (pH 1.2, 4.5, 6.8, 7.4, 8.0 and TDW) was

added. These suspensions were left for shaking on a platform shaker for 48 h at 25±2^{O}C. Solutions were then filtered through Whatman filter paper No 41 and analyzed after suitable dilution with phosphate buffer pH 7.4 at 12, 24 and 48 h using the developed UV analytical method.

Determination of λ max: Indomethacin was dissolved in the ratio of Methanol: Phosphate buffer (PH 7.4) in ratio of (10:90% v/v) and scanned for maximum absorbance in UV Spectrophotometer (Double beam) in U. V. range i.e., from 200 to 400 nm. The Spectra of Indomethacin showed the maximum absorbance at 320 nm.

Preparation of Standard Curve: Aliquot of drug from secondary stock solution ranging from 0.2ml to 1.2ml were transferred in to 10ml volumetric flask and were diluted up to the mark with pH 1.2 and pH 7.4 phosphate buffer separately to get a final concentration ranges from 2-12µg/ml. Absorbance of each solution was measured at 320nm. A plot of concentrations of drug versus absorbance was plotted.

Compatibility study: The FTIR absorption spectra of pure Indomethacin, permeation enhancer, polymers (HPMCK15M, PVPK30, and EC) and also combined mixture of drugs and polymer were measured by Shimadzu &ATR spectrophotometer.

2.2 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 HPMCK15M, PVPK30, 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 cm2 were prepared by cutting and packed in an aluminum foil and kept in a desiccator.

Table 1: Composition of Transdermal patches

Formulation Code	Drug (mg)	HPMCK15M (mg)	PVP K30(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(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)

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

Table 2: 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

Evaluation of Transdermal Patches: using standard methods of Thickness of patches, weight variation, drug content, % moisture content, % Moisture absorption/uptake, Swelling index, Folding endurance, Percentage Elongation, Tensile Strength, *In-vitro* permeation studies, Drug release kinetics and Stability studies.

3. RESULTS AND DISCUSSION

3.1 Preformulation studies:

The Indomethacin sample is awhite color powder having Melting Point at 160°C. Drug is very soluble in ethanol, methanol, and acetone and slightly soluble in acetonitrile and practically insoluble in water. Studies revealed that the drug that was present in a micronized form had a solubility of 53.5 ± 0.15 µg/ml at 25°C in distilled water. The drug was shown to have pH dependent solubility with solubility increasing from very low value of 2.8 ± 0.02 µg/ml (pH 1.2) to 4.5 ± 0.02 µg/ml (pH 4.5) and 1023.6 ± 3.56 µg/ml at pH 7.4.With increase in pH, increase in protonation (ionization) of carboxylic acid moiety resulted in abrupt increase in solubility of indomethacin in alkaline pH. Further, increase in pH to 8.0 was not found to increase solubility. Therefore, according to the USP solubility definition, indomethacin has been shown as a practically insoluble drug at pH 1.2 and slightly soluble at pH 7.4. The λ max of indomethacin in phosphate buffer (pH 7.4) was found to be at 220 nm with a second peak at 266 nm and third peak at 320 nm. The wavelength selected for estimation purpose was 320 nm as there was no interference from excipients at this wavelength.

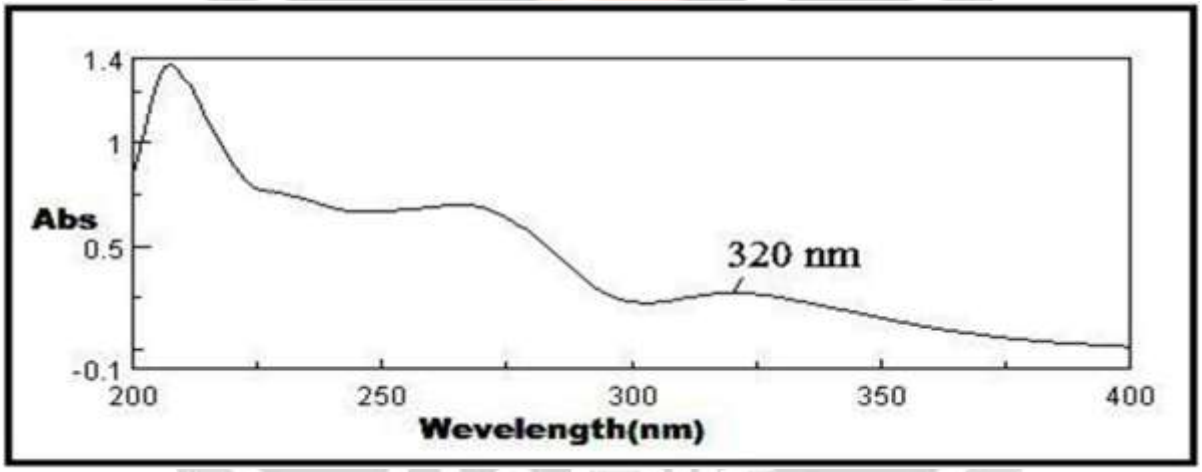

Figure 1: UV Absorbance Spectra of indomethacin in phosphate buffer pH 7.4

Standard curve of Indomethacin: The standard curve for Indomethacin in PBS pH 7.4 was made. The method followed Beer's law limit in the proportions range of 2-14 mcg/ml at 320 nm with a R2 value of 0.996.

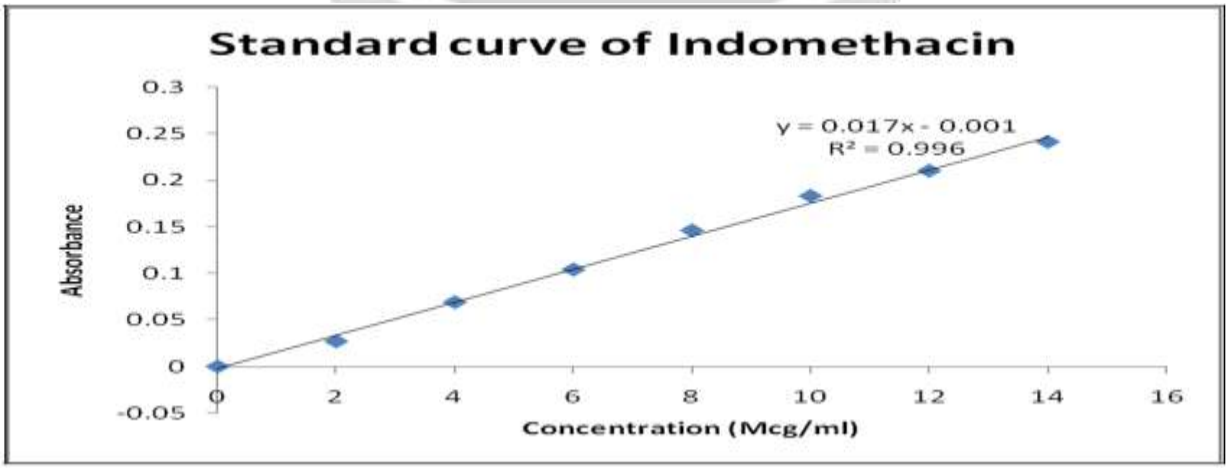

Figure 2: Standard curve of Indomethacin using Phosphate buffer 7.4 pH at 320 nm

Fourier Transform-Infrared Ray Spectroscopy Studies (FT-IR) Studies: Drug polymer compatibility studies were carried out using FT-IR spectroscopy to establish any possible interaction of Indomethacin drug with the excipients and natural permeation enhancers used in the formulation. 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.

3.2 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 indomethacin drug showed different peaks e.g. O–H stretching (Alcohol of carboxylic acid) at 3355, C–H stretching (Alkane group (-CH3) at 3054, C=O stretching (Carbonyl group) at 1741, aromatic C=C stretching at 1647 and C-O stretching (ether group) at 1410, cm–1 which confirms the purity of the indomethacin drug. Same peaks are also found in the FT-IR Spectra of the formulations mixtures (Indomethacin+HPMC+PVP+EC +PEG-400) and (Indomethacin+HPMC+PVP+EC+PEG-400+Camphor+OLEIC ACID + Menthol), showing that no drug–polymer interaction seen. In FT–IR studies the characteristic peak due to pure indomethacin has appeared in the spectra of formulations mixtures. The identical peaks are also present in drug loaded HPMC, PVP, Ethyl Cellulose (EC), and PEG-400, camphor and oleic acid mixed as polymeric formulations mixtures. All the characteristic peaks of indomethacin are present FT-IR 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: FT-IR of Indomethacin

Wave number (cm^{-1})	Due to	Functional Group	Indomethacin	Transdermal Patch	With penetration enhancer
3700-2500	Alcohol of carboxylic acid	O-H str.	3355	3392	3264
3000-2800	Alkane group(-CH3)	C-H str.	3054	3057, 3027, 2933	3053, 2834
1760	Carbonyl group	C=O str.	1741	1890	1741
1600	Carbon- carbon double bond	C = C str.	1647	1672	1655
1450	Ether	CH3- O str.	1410	1445	1435

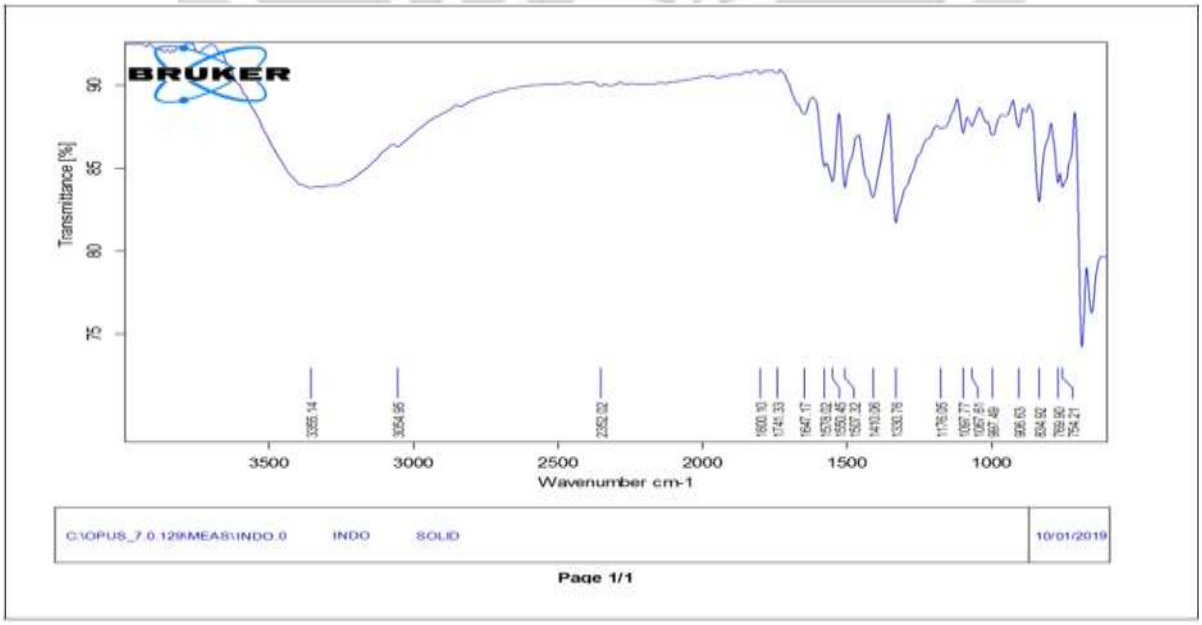

Figure 3: FT-IR of Indomethacin

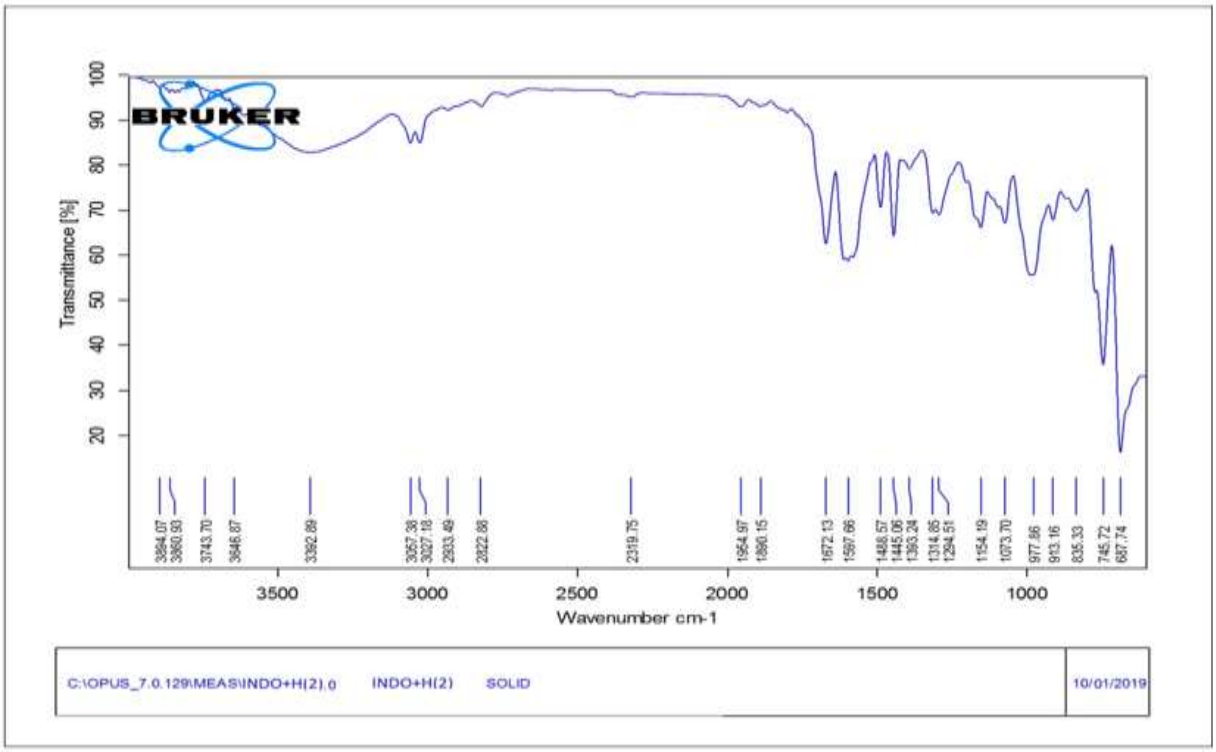

Figure 4: FTIR of Transdermal Patch containing Indomethacin

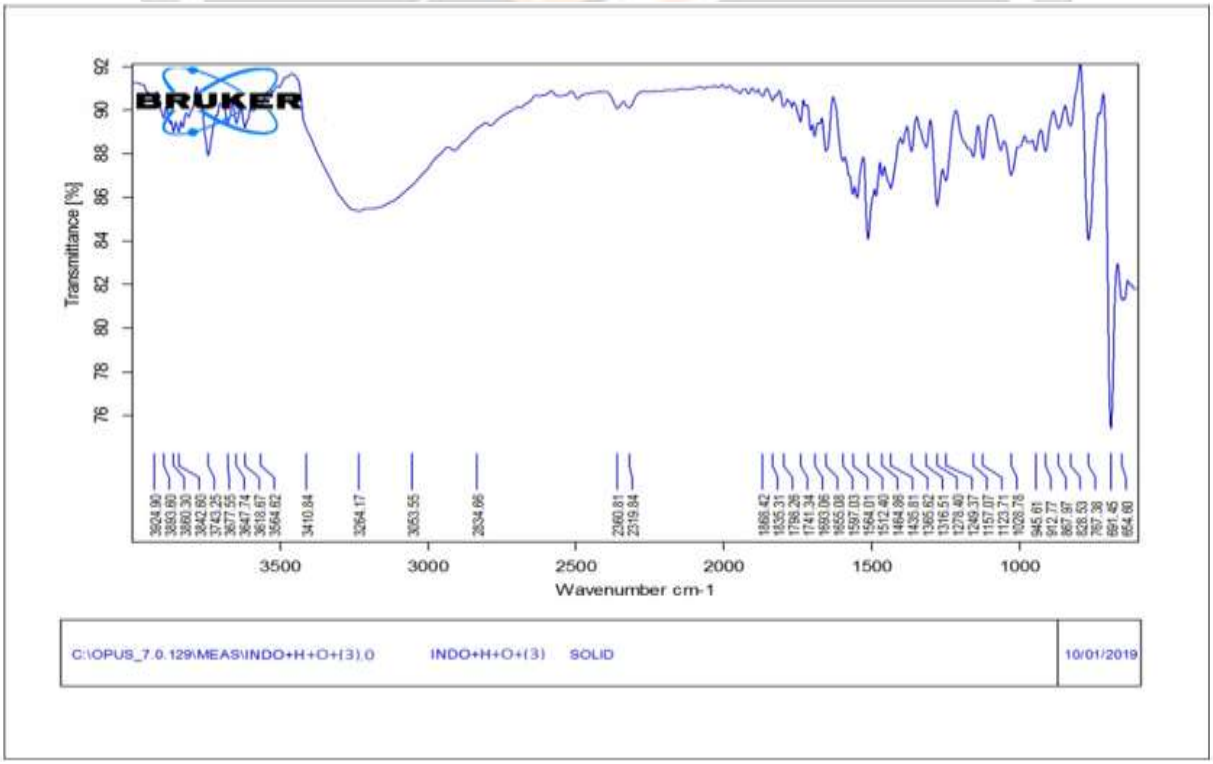

Figure 5: FT-IR of Indomethacin Transdermal Patch of Camphor, Oleic acid and Menthol

Physical Evaluation of Transdermal Patches: Table shows the physicochemical evaluation like the Thickness, Folding endurance, Percentage moisture absorbed, Percentage moisture lost, Drug content uniformity.

Table 4: Physical Evaluation data of Indomethacin Transdermal Patches

Formulation Code	Thickness (mm)	Weight variation (mg)	% Drug Content Indomethacin	Folding endurance	Tensile strength Kg/mm2
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 5: Physicochemical Evaluation data of Indomethacin Transdermal Patches

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

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. The drug permeation data of F5 was plotted for Zero order, First order, Higuchi model and Korsmeyer-Peppas model to evaluate the permeation pattern of the dosage form. 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.

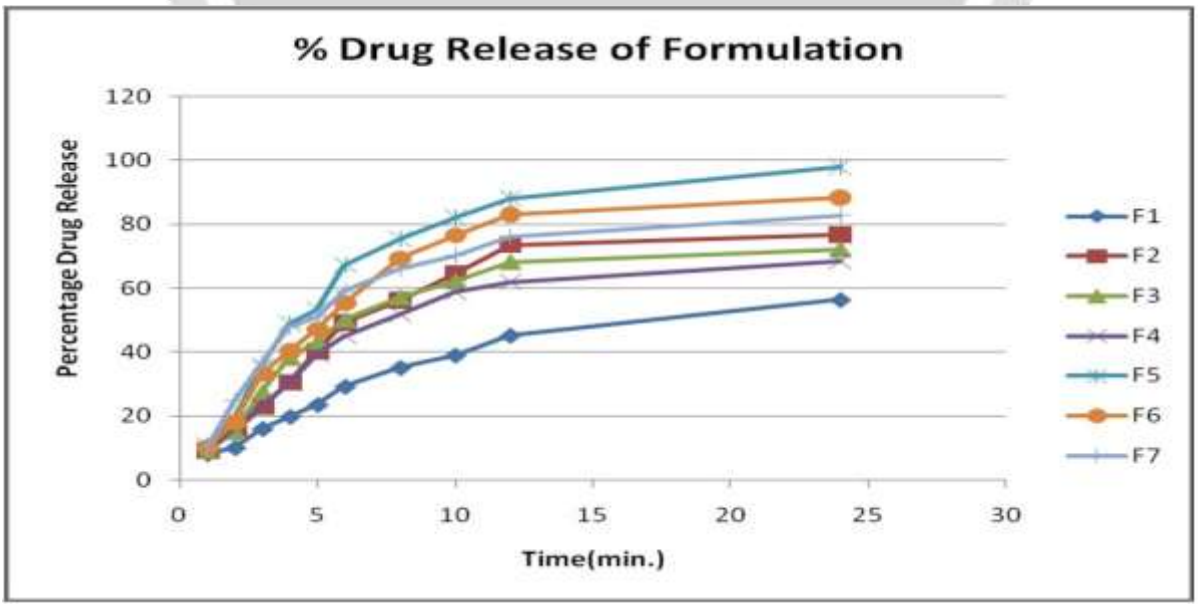

Figure 6: *In-vitro* Drug Permeation Indomethacin of F1 to F7

Table 6: 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

3.3 Drug release kinetic modeling of optimized formula

On comparison of kinetic modeling and release profile data it was evident that Transdermal Patch containing Indomethacin was found to release the drug in accordance to first order kinetics, the regression coefficient was not found to be exactly near to 1, which could be due to influence of some other factors.

Table 7: R^2 value of optimized formulation TF5

Model Name	Zero order	Fist order	Higuchi model	Hixson	Korsemeyer -Peppas	Best fit model
R^2 value of F5 for Indomethacin	0.727	0.995	0.919	0.935	0.762	First order kinetics model

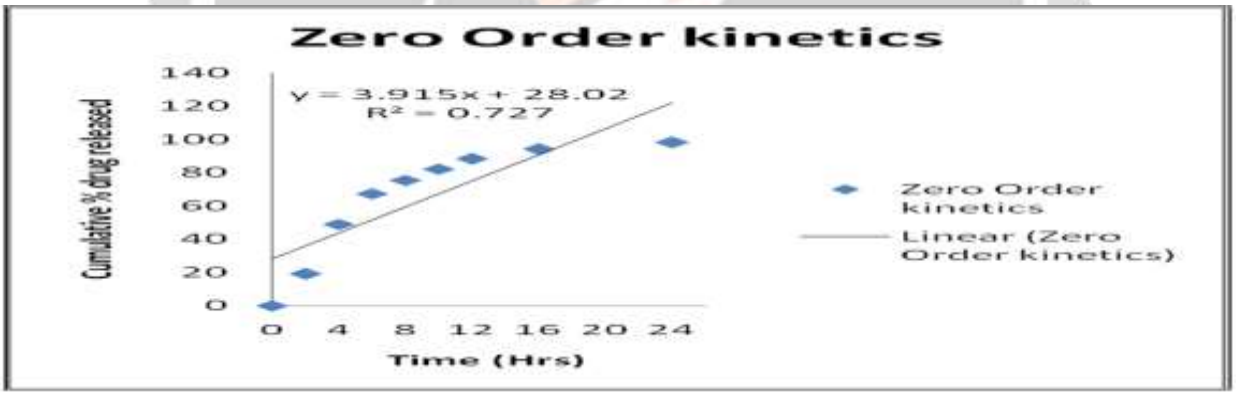

Figure 7: Zero order Kinetic Model for Indomethacin Trasdermal Patch formulation F-5

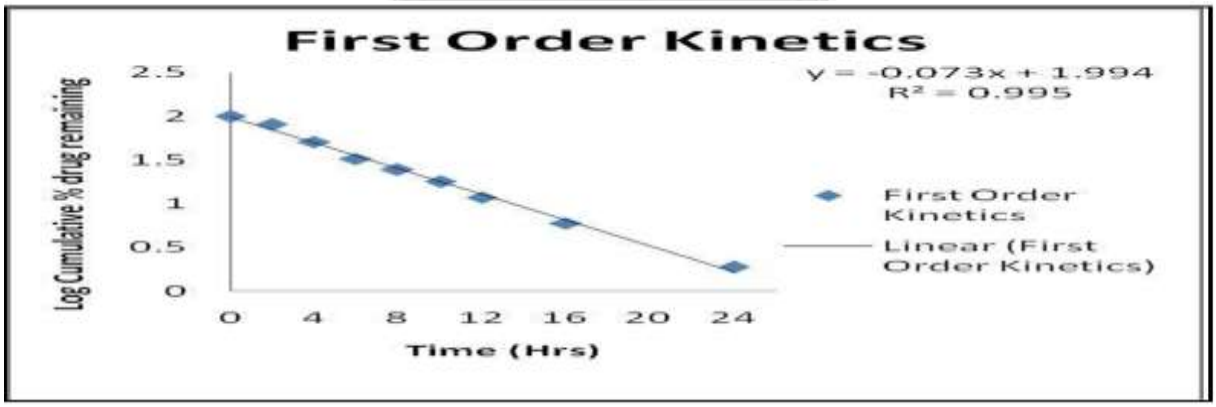

Figure 8: First order Kinetic Model for Indomethacin Trasdermal Patch formulation F-5

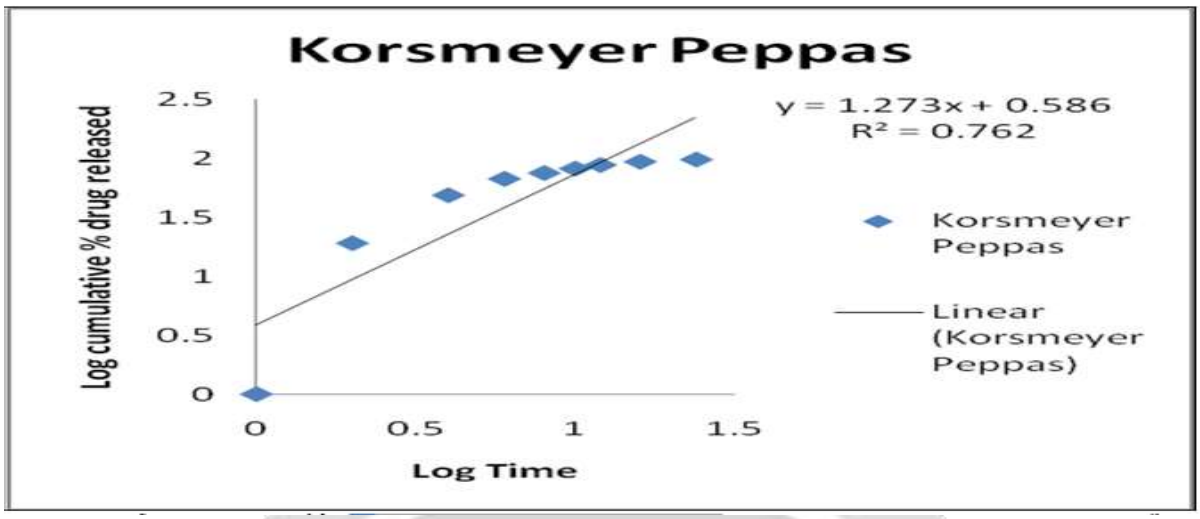

Figure 9:Korsmeyer peppas Model for Indomethacin Trasdermal Patch formulation F-5

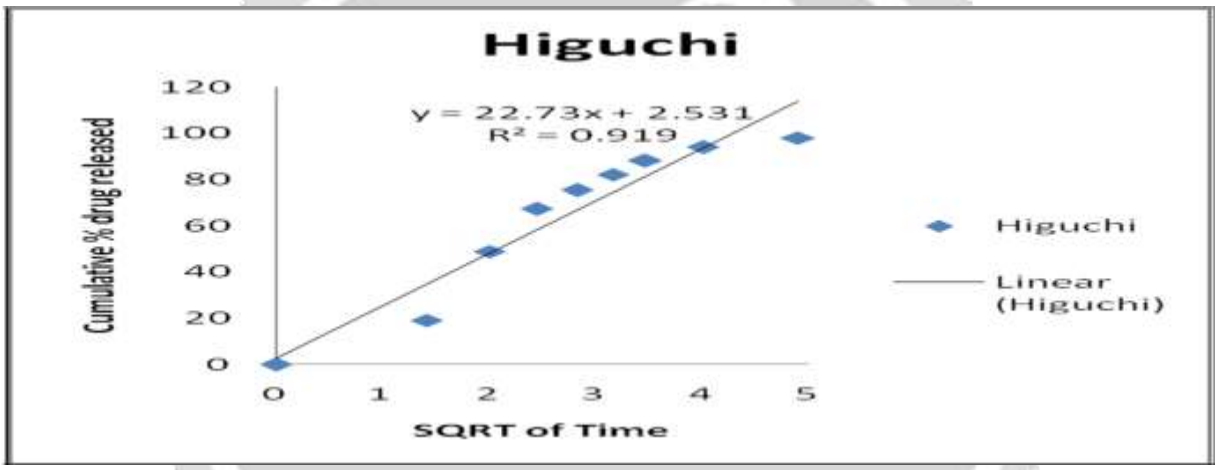

Figure 10: Higuchi Model for Indomethacin Trasdermal Patch formulation F-5

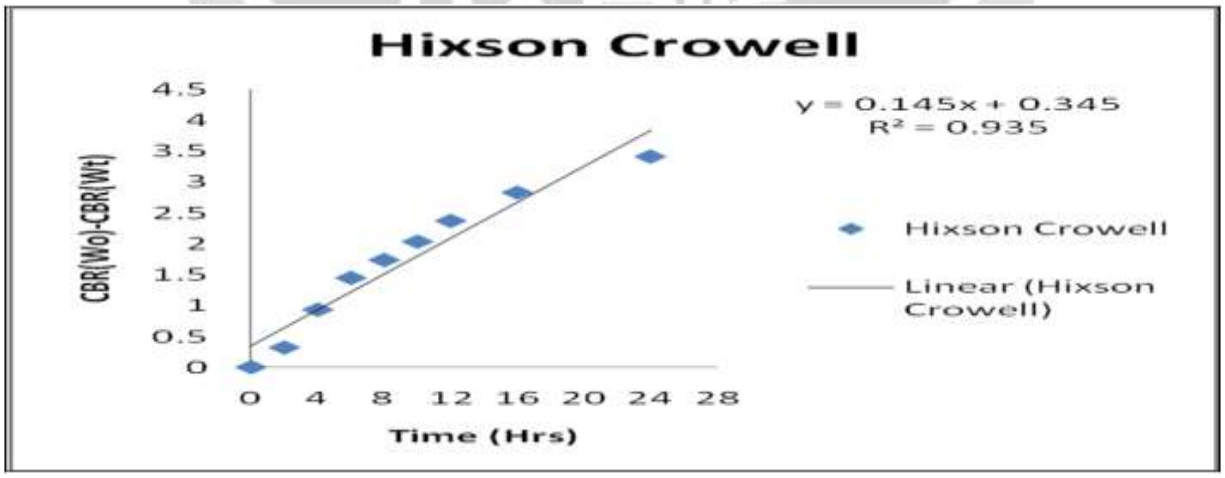

Figure 11: Hixson Crowell Model for Indomethacin Trasdermal Patch formulation F-5

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. The selected formulations namely F5 was subjected for stability studies as per ICH guidelines and observed for all evaluation parameters at a

temperature of 250C and 60% RH, 400C and 75% RH, at an interval of three month. There were no physical changes in flexibility and physicochemical evaluation parameter was slightly changed.

Table 8: Stability Study of Indomethacin TDDS batch F5

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 Indomethacin	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

4. CONCLUSIONS

TDDS are the ideal delivery system for drugs that undergo hepatic first pass metabolism. In the present study, an attempt was made to prepare, characterize and evaluate of transdermal matrix patches of Indomethacin 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 HPMCK15M, PVPK30, 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.

5. CONFLICTS OF INTERESTS

There are no conflicts of interests

6. REFERENCES

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