

Formulation Development And Evaluation Of Transdermal Patch By Using Natural Polymer And Niaouli Oil As A Permeation Enhancer

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Keywords:	ABSTRACT
Skin Penetration, Improved Bioavailability, First Pass Metabolism, Better Patient Compliance	Since oral bioavailability of Isradipine is poor due to high first pass metabolism different matrix. Transdermal applications, relative to other routes, are non-invasive, requiring the simple adhesion of a “patch” resulting in better patient compliance, improved bioavailability of a drug, and easy treatment termination. Hence, this investigation, aimed at delivering Isradipine across intact skin as a membrane-moderated transdermal therapeutic system of Eudragit R100. Optimized batch was evaluated for permeation enhancement through rat skin using natural permeation enhancer Niaouli oil and it can concluded that permeation enhancement through Skin. Niaouli oil comparable to commercially available permeation enhancer DMSO.

1. Introduction

Transdermal drug delivery systems (TDDS) offer a non-invasive and effective alternative to traditional oral and injectable routes, enabling controlled and sustained release of therapeutic agents while minimizing first-pass metabolism. However, the stratum corneum, the outermost layer of the skin, presents a formidable barrier to drug permeation. To overcome this challenge, the development of transdermal patches incorporating natural polymers and permeation enhancers has garnered significant attention. Natural polymers, such as psyllium, hydroxypropyl methylcellulose (HPMC), and flaxseed mucilage, are increasingly utilized in TDDS due to their biocompatibility, biodegradability, and non-toxicity. These polymers not only serve as matrix formers but also contribute to the controlled release of active pharmaceutical ingredients (APIs). For instance, studies have demonstrated the successful formulation of transdermal patches using natural polymers, achieving desired drug release profiles and skin compatibility. In parallel, the incorporation of natural permeation enhancers, such as essential oils, has shown promise in enhancing drug permeation through the skin. Niaouli oil, derived from the leaves and twigs of *Melaleuca quinquenervia*, is rich in terpenes like 1, 8-cineole, α -pinene, and limonene, which have been identified as effective skin penetration enhancers. Research indicates that niaouli oil can significantly increase the transdermal flux of model drugs like estradiol, surpassing other essential oils in efficacy [1].

The synergistic combination of natural polymers and niaouli oil in transdermal patch formulations aims to harness the benefits of both components: the structural integrity and controlled release properties of natural polymers, and the enhanced skin permeation facilitated by niaouli oil. This approach not only improves the therapeutic efficacy of the delivered drug but also aligns with the growing preference for natural and sustainable pharmaceutical formulations [2].

2 Materials and methods

2.1 Materials:

Isradipine as a gift sample by Akums Pvt. Ltd., India, Niaouli Oil Extracted in-house from the leaves and twigs of *Melaleuca quinquenervia* (Niaouli) through steam distillation, Eudragit L100 sourced from

Sarvodaya Enclave, New Delhi, India, Propylene Glycol as aplasticizer, obtained from Sigma-Aldrich, India, Xanthan Gum, purchased from HiMedia Laboratories, India, Almond Gum obtained from the Sigma-Aldrich, India and Dimethyl Sulfoxide (DMSO) from Sigma-Aldrich, India.

2.2 Pre-formulation Studies:

2.2.1 Methods:

2.2.1.1 Extraction of Niaouli oil:

The shade dried leaves were subjected to size reduction and passed in to sieve no 20 and then 40. About 500g of the dried powder was extracted continuously in Soxhlet apparatus with methanol for 72 hours to obtain the crude extract. The extract was dried under vacuum oven [3].

2.2.2 FTIR Studies:

The application of infrared spectroscopy lies more in the qualitative identification of substances either in pure form or in the mixture and as a tool in establishment of the structure. Since I.R. is related to covalent bonds, the spectra can provide detailed information about the structure of molecular compounds. In order to establish this point, comparisons were made between the spectrum of the substance and the pure compound. The infrared data is helpful to confirm the identity of the drug and to detect the interaction of the drug with the polymer. Infrared spectra of drug and polymer, alone and in physical mixtures were taken. Then it was investigated for any possible interaction between polymer and the drug [4].

2.2.3 Determination of λ_{max} :

For assurance of λ_{max} stock solution of Isradipine (Conc. 1000 μ g/ml) in methanol were readied. 1ml of the readied stock arrangement was additionally weakened to 100ml. Coming about arrangements were examined in the range of 540 to 556nm utilizing methanol as a clear with the assistance of a UV-visible spectrophotometer. Normal triplicate readings were taken [5, 6].

2.2.3.1 Calibration curve of Isradipine in pH-6.8 phosphate buffer:

The above stock arrangement filtered for the most extreme absorbance utilizing UV max of Isradipine in phosphate buffer pH 6.8 was seen as 543nm. The above stock arrangement (100g/ml) was additionally weakened to get focus in the range of 10-50g/ml. The absorbance of every arrangement was estimated utilizing a UV-Visible double beam spectrophotometer by putting reference standards of a particular medium. The standard bend produced for a whole range of conc. and the tests acted in triplicate [7].

2.3 Preparation of Transdermal Patch Solvent Casting Method:

An accurately weighted quantity 1.75g of Almond gum (17.5% w/w) was soaked in distilled water (10 ml) for 4 h. After swelling of the gel, drug solution in distilled water and methanol containing 2 mg/g of drug isradipine was incorporated into gel separately with continuous mixing in a blender. Compositions of different Transdermal reservoir systems containing isradipine are showed in below Table.1 [8, 9].

Table.1: Formulation of transdermal patches of Isradipine

Formulation Code					
Ingredients	F1 (1:1)	F2 (1:2)	F3 (1:2)	F4 (1:3)	F5 (1:2)

Drugs (Mg)	2	2	2	2	2
Almond Gum	-	-		10	15
Xanthum Gum	-	-	15	-	-
Niaouli oil	-	-	2.5	5	10
DSMO	2.5	5	-	-	-
Eudragit R 100	2	2.5	3	3.5	5
Propylene Glycol	22.5	15	7.5	10	5
Methanol	3	3	3	3	3
Glycerol	Q.S	Q.S	Q.S	Q.S	Q.S

2.4 Evaluation of Transdermal Patch:

2.4.1 Physical Appearance:

All the transdermal patches were visually inspected for colour, clarity, flexibility, and smoothness.

2.4.2 Weight Variation:

This was done by weighing five different patches of individual batch taking the uniform size at random and calculating the average weight. The tests were performed on patch which was dried at 60°C for 4 hr prior to testing [10].

2.4.3 Thickness of the Patch:

The thicknesses of the patches were assessed by using digital Vernier calliper at different points of the patch. From each formulation three randomly selected patches were used. The average value for thickness of a single patch was determined [11].

2.4.4 % Drug Content:

The patches (2×1cm²) were taken and cut into small pieces, added to a beaker containing 100 ml of distilled water the medium was stirred magnetic bead for 5hrs. The solution was filtered and analysed for drug content with proper dilution at 543nm U.V spectrophotometrically [12].

2.4.5 Folding Endurance:

This was determined by repeatedly folding one patch at the same place till it broke. The number of times the patch could be folded at the same place without breaking gave the value of folding endurance [13-14].

2.4.6 % Moisture Uptake:

The patches were weighed accurately and placed in desiccators containing aluminium chloride. After 24 hr, the patches were taken out and weighed. The percentage moisture uptake was calculated as the difference between final and initial weight. It was calculated by using following formula [15].

$$\% \text{ moisture uptake} = [\text{Final weight} - \text{Initial weight} / \text{Initial weight}] \times 100$$

2.4.7 Determination of Surface pH:

The patches were allowed to swell by keeping them in contact with 5ml of distilled water for 2hr at room temperature and pH was noted down by bringing the electrode in contact with the surface of the patches, allowing it to equilibrate for 1min [16].

2.4.8 Tensile Strength and % Elongation:

Tensile strength of the patches was determined with Universal strength Testing Machine. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The patches of size (2×1cm²) were fixed between these cell grips and force was gradually applied till the patches broke. The tensile strength of the patches was taken directly from the dial range reading in kg [17-18].

2.5 In-vitro Skin permeation study:

In-vitro diffusion study was performed by using a Franz diffusion cell with a receptor compartment of 250ml. The cellophane membrane was mounted between the donor and the receptor compartment of the diffusion cell. The formulated patches were cut in size of (2×1cm²) and placed over the cellophane membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 100 rpm; The temperature was maintained at 37±0.50°C. The samples of 5ml were withdrawn at the time interval of 1hr up to 21 hr and analysed for drug content U.V spectrophotometrically at 310nm against blank. The receptor medium was replaced with an equal volume of phosphate buffer pH 7.4 at each time of sample withdrawal. The cumulative amounts of drug permitted were plotted against time [19].

2.6 Skin irritation test:

Skin irritation test was done to check that the formulation is free from any skin irritation. Male Wistar rats were selected for this study. One day before of the experiment, hairs on back of rats were removed by clipping. 5 groups were prepared each of 6 Rats per group and were treated one time in a day over a period of 7 days. Group 1- Normal, Group 2- control (application of commercially available formulation), Group 3- 0.8% v/v aqueous solution of Formalin (Formalin was used as a standard irritant with concentration of 0.8% v/v.), Group 4 blank transdermal patch (without drug), Group 5- Transdermal patch with a drug. Application site will be evaluated on 8th day by same investigator for erythema and oedema [20].

2.7 Diffusion Kinetics:

To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to Zero order, First, Higuchi matrix, Korsmeyer's Peppas's model. By comparing the r²-values obtained, the best model was selected [60].

2.8 Scanning Electron Microscopy (SEM):

The exterior surface characteristics of received sample (semi solid; constituents along with presence of polymer) were examined by Scanning electron microscope. The sample was placed on plain glass stub and sputter coating of gold was done to make surface of particles electro-conductive. Images were recorded using SEM equipped with SEM digital camera [21].

2.9 Stability Studies:

Optimised formulation F4 was subjected to accelerated stability study at 40±2°C and 75±5 % RH for 1, 2 & 3-months. The Isradipine Loaded Transdermal Patch is evaluated for description, Color and Folding Endurance and % Drug Content and In-Vitro Drug [21].

Results and Discussion

3.1 Preformulation Studies:

3.1.1 FTIR Studies:

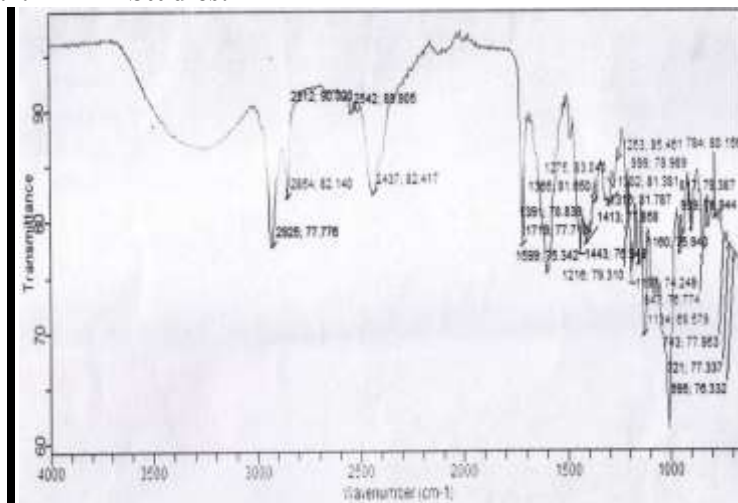


Fig.1: FTIR Spectra of Isradipine

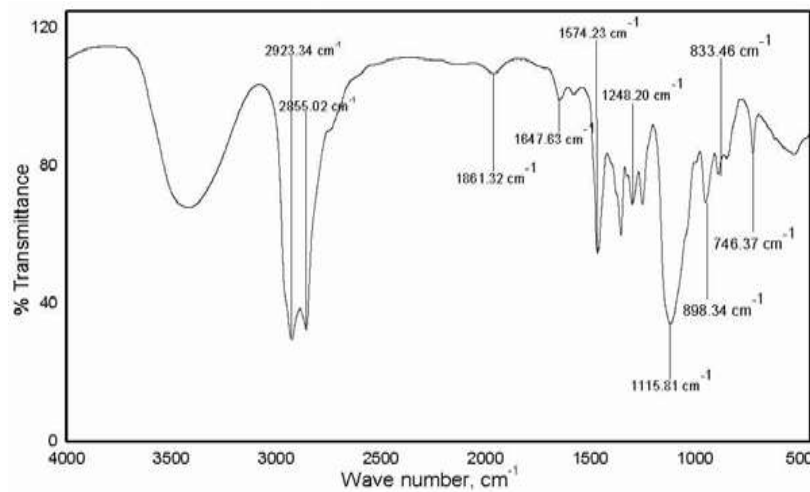


Fig.2: FTIR Spectra of Isradipine and niaouli oil

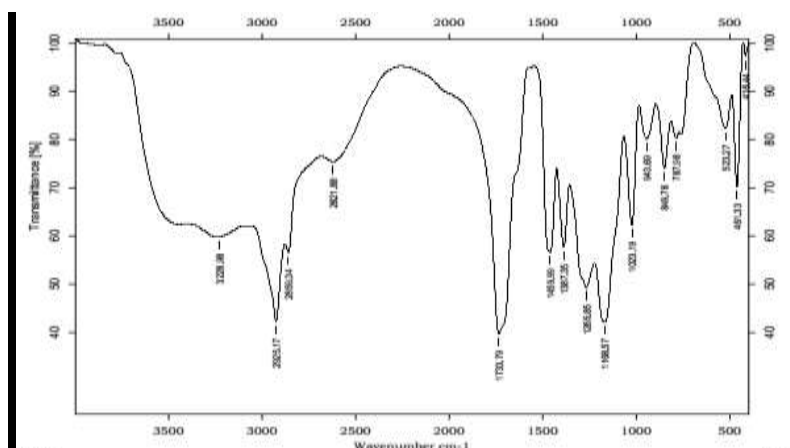


Fig.3: FTIR Spectra of Isradipine +Eudragit

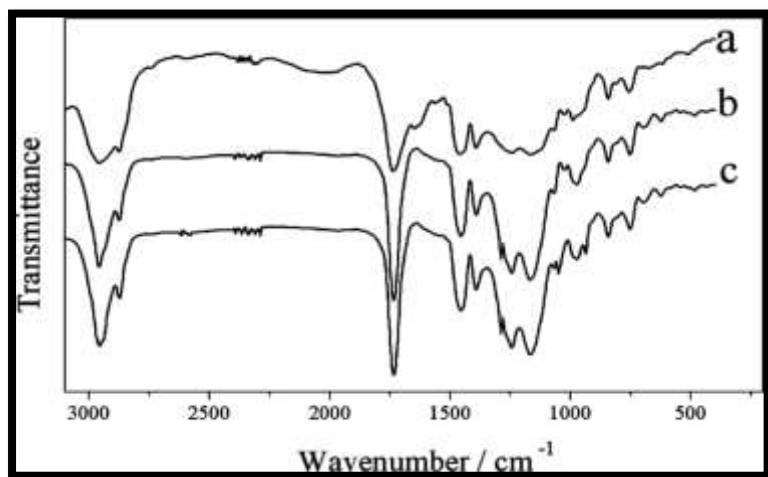


Fig.4: FTIR Spectra of Isradipine+PEG-400+ Xanthum Gum

Table.2 FTIR Spectrum

Functional Groups	Reported frequency cm^{-1}	Observed Frequencies cm^{-1}
O-H group	3400-2400	2400
C- H stretching	3150-3050	2854.24
CH ₂ stretching	3409-3389	3043.43
NH ₂ stretching	3270-3043	3193.34
C-H stretching	3032-2980	3267.56
R-O-CH ₃ stretching	3645-3590	3589.23

3.1.2 Determination of λ_{max} :

Table.3: Data of concentrations and absorbance in phosphate buffer pH 6.8

S. No.	Concentration ($\mu\text{g/ml}$)	Absorbance
1	2	0.31
2	4	0.509
3	6	0.749
4	8	1.01
5	10	1.241
6	12	1.298

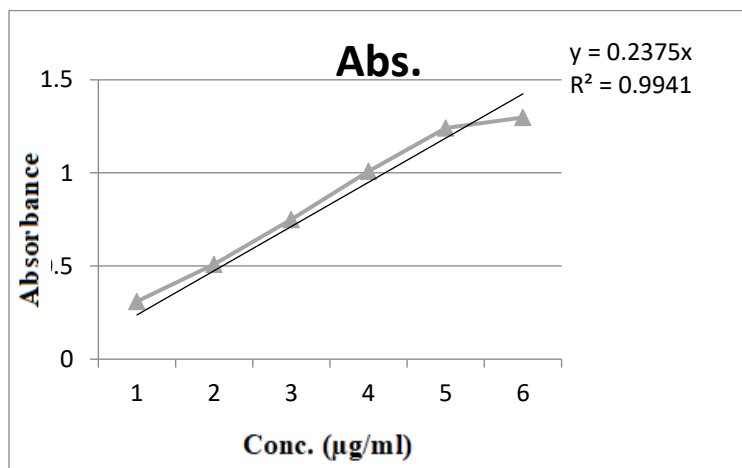


Fig.5: Calibration curve of Isradipine in phosphate buffer pH 6.8

3.2 Evaluation of Isradipine Transdermal Patch:

Table.4 Organoleptic Property Analysis of Developed Transdermal Patches

S.No	Physical Appearance	Result
1	Appearance	Jellified Preparation
2	Color	Pale Yellow
3	Clarity	Opaque
4	Flexibility	Good
5	Smoothness	Fair

Table.5 All Evaluation Parameters

Formulation	Weight Variation	Thickness	% Drug Content	Folding Endurance	% Moisture Uptake	pH	Tensile Strength	% Elongation
F1	0.643±0.013	0.108±0.005	90.02±1.21	142±2.5	1.90±0.05	6.4±0.11	0.380±0.010	32.33±1.312
F2	0.812±0.030	0.114±0.034	91.84±0.690	198±1.6	2.78±0.06	5.8±0.14	0.404±0.008	30.51±0.422
F3	0.787±0.041	0.130±0.021	94.16±0.332	110±6.0	2.64±0.014	5.6±0.10	0.217±0.012	28.51±1.562

F4	0.870±0.095	0.242±0.012	98.58±0.922	66±2.2	1.90±0.012	5.2±0.15	0.235±0.011	22.51±1.160
F5	0.982±0.092	0.290±0.014	96.56±0.922	74±2.7	1.80±0.016	5.1±0.14	0.215±0.014	24.51±1.160

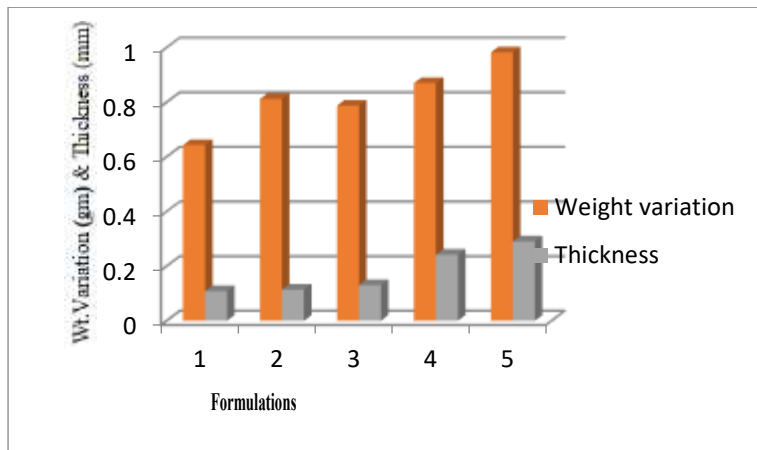


Fig.6: Evaluation Transdermal Patch of (weight variation and thickness)

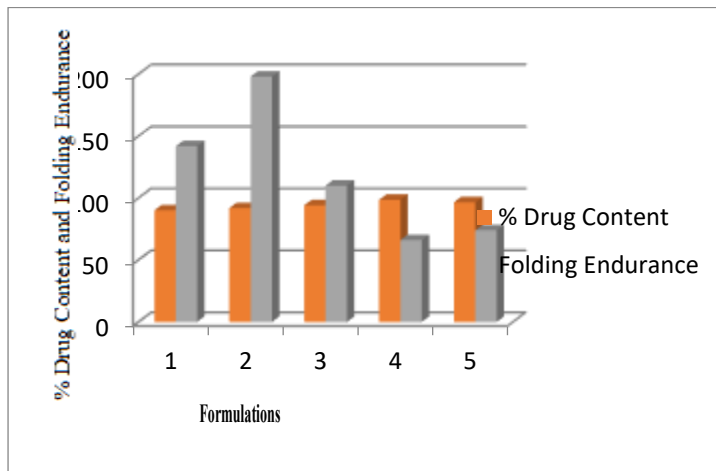


Fig.7: Evaluation Transdermal patch of % Drug Content and Folding Endurance

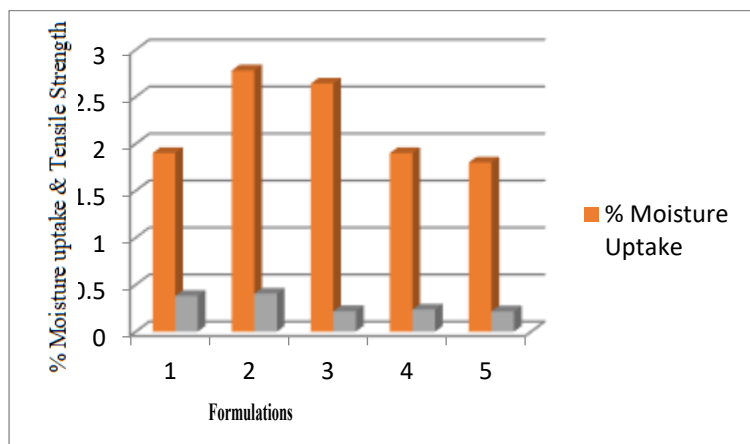


Fig.8: Evaluation Transdermal patch of (% Moisture uptake & Tensile Strength)

3.3 In-vitro Diffusion Studies:

The in-vitro diffusion drug studies of patches F1 to F5 were performed by using cellophane membrane in Franz diffusion cell for 24hrs. The percentage of drug release across cellophane membrane for the formulations F1 to F5 were found to be at the end of 24 hrs F1 (72.87±0.02%), F2 (80.83±0.18%), F3 (90.10±0.04%), F4 (98.1±0.02%) and F5 (96.4±0.03%), at the end of 24 hrs, but F5 showed maximum drug release i.e. 96.4±0.3% at the end of 10hrs. It was revealed from the below results that with increasing in the concentration of Eudragit L100 and Niaouli, the drug release from the patch increased.

Table.6 In-vitro Diffusion Studies

Time (Hrs)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	28.34±0.06	30.34±0.12	35.76±0.06	38.67±0.01	34.45±0.02
10	39.67±0.20	45.67±0.15	48.45±0.02	54.34±0.06	52.9±0.07
15	48.90±0.12	54.63±0.09	60.23±0.03	68.9±0.05	69.4±0.08
20	58.94±0.09	72.87±0.17	78.43±0.04	84.2±0.09	81.24±0.04
25	72.87±0.02	80.83±0.18	90.10±0.04	98.1±0.02	96.4±0.03

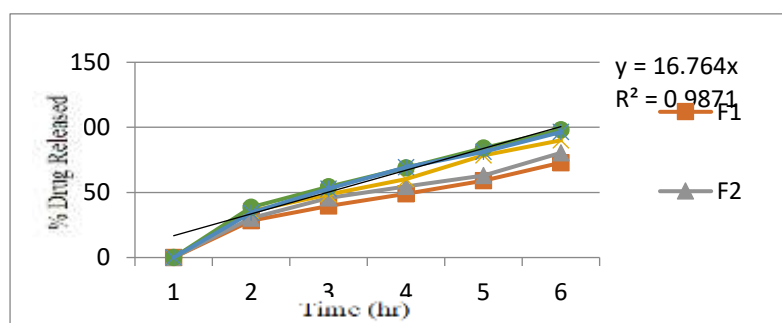


Fig.9: In-vitro Diffusion Drug Studies of Patches F1 to F5

3.4 Diffusion Kinetics:

To know the mechanism of drug release, the data were fitted to models representing Zero-order, First-order, Higuchi and Korsmeyer-Peppas. It was found that the release of patches followed zero order kinetics. The coefficient of determination (F4) was found to be much closer to 1 for the Korsmeyer-Peppas equation. Slope values ($n > 1.0$) suggest that the drug permeation from Transdermal patches followed the non-Fickian diffusion mechanism, possibly owing to chain disentanglement and swelling of hydrophilic polymer.

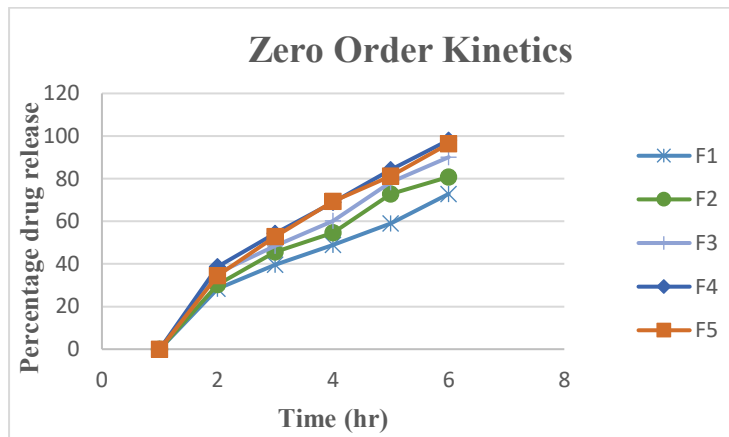


Fig.10: Zero-order release kinetics

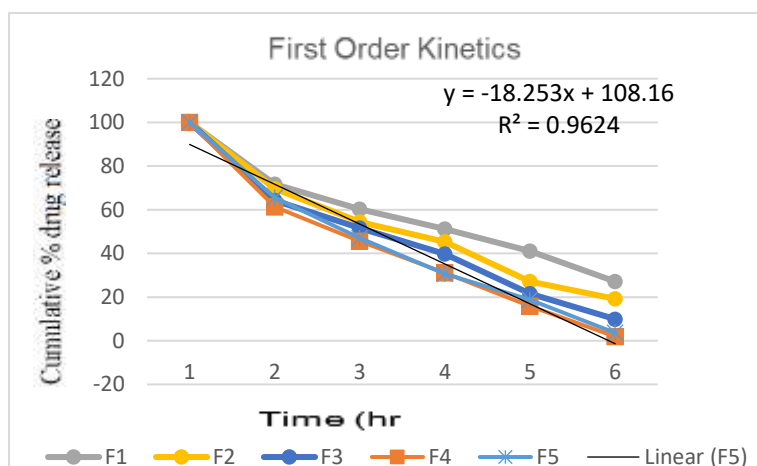


Fig.11: 1st-order release kinetics

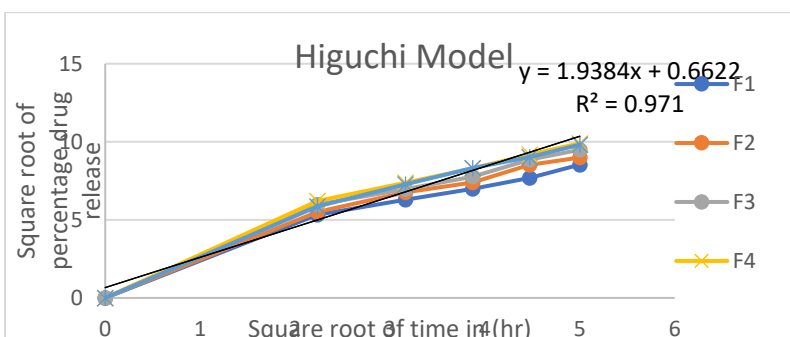


Fig.12: Higuchi Model unleash Kinetics

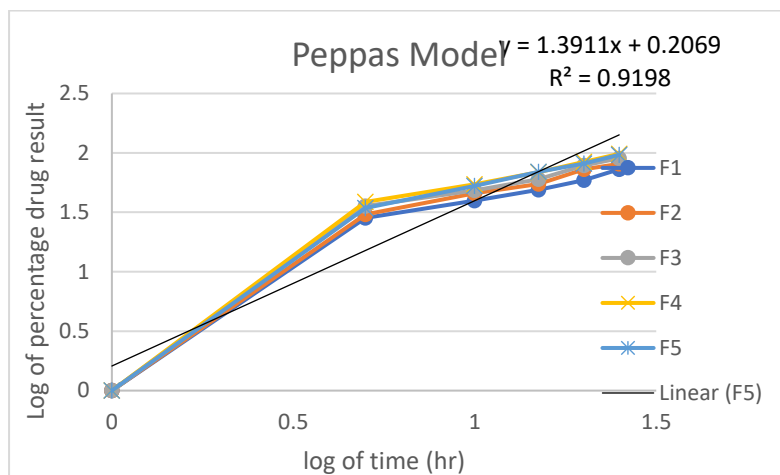


Fig.13: Peppas Model Release Kinetics

3.4.1 Release Kinetics for Isradipine Transdermal Patch:

Table.7: Release kinetics for all of Isradipine Transdermal

Formulation code	Zero-order	1 st -order	Higuchi	Peppas
	r ²	r ²	r ²	r ²
F1	0.954	0.954	0.960	0.915
F2	0.958	0.958	0.967	0.919
F3	0.957	0.957	0.962	0.910
F4	0.954	0.954	0.962	0.908
F5	0.949	0.962	0.971	0.919

Discussion:

Formulations F2 and F5 demonstrate the best overall release kinetics across the models, with consistently high r^2 values. F2, in particular, shows a strong fit to zero-order kinetics, suggesting a controlled and sustained release profile. F5 exhibits the highest r^2 values in the Higuchi and Korsmeyer–Peppas models, indicating a complex release mechanism involving both diffusion and erosion.

3.5 Skin Irritation Study:

Visual evaluation was done for skin irritation test. It was observed that erythematic and edema observed in the group 4 was not more as compare to the group which was treated with standard irritant i. e. aqueous Formalin solution 0.8% v/v. So, it can be concluded that formulation having no skin irritation or very little amount of irritation.

3.6 Scanning Electron Microscopy (SEM):

The morphological features acquired from optimized formulation was photographed using SEM. Images shown presence of irregular shaped crystals with presence of aggregations. Rationales may be attributed to precipitation of the sample.

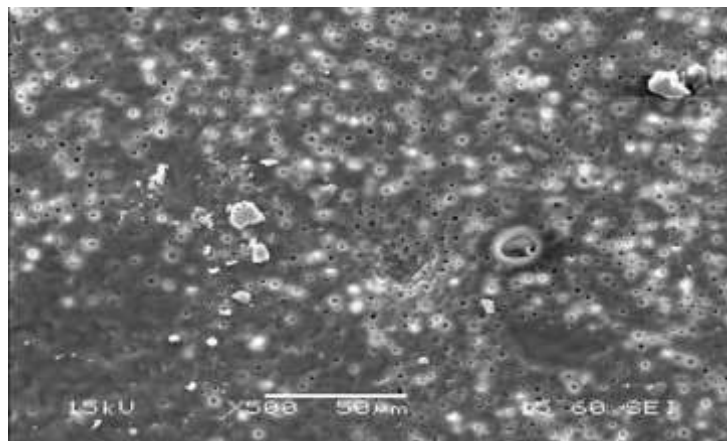


Fig.14: Morphology of Isradipine Loaded Transdermal Patch, as viewed by SEM

3.7 Stability Studies Results of Optimized Batch F4:

Table.8 Stability Studies of Selected Formulation F4

Evaluation Parameters	Initial	15-Days	1-Month	3 Month
Color	Pale Yellow	Pale Yellow	Pale Yellow	Pale Yellow
Folding Endurance	66±2.7	66±2.5	66±2.0	65±2.5
% Drug Content	96.56±0.903	96.45±0.900	96.32±0.897	95.68±0.858
In-Vitro Drug Release Study	98.1±0.02	98.0±0.01	97.90±0.02	97.10±0.03

CONCLUSION

The Transdermal patches of Neem (methanolic extract) (F1, F2, F3, F4 and F5) were successfully prepared by solvent casting method using Niouli as a permeation enhancer and Eudragit L100 in 1:1.1:2, 1:2, 1:3 and 1:4 ratios. The FTIR studies did not reveal any significant drug interactions. The prepared patches showed good results for physicochemical evaluations, in-vitro diffusion studies and skin irritation study. On comparing major in evaluation criteria, formulation F4 was selected as best formulation. The release kinetics of all the patches showed zero-order kinetics and followed non-Fickian diffusion mechanism. The skin irritation study showed that there is a no skin side effect of this patch with skin. As we know that distribution of drug via skin is not easy there is various factors that could be affect the drug absorption. Optimized batch was evaluated for permeation enhancement through rat skin using natural permeation enhancer Niaouli oil and it can concluded that permeation enhancement through Skin. Niaouli oil comparable to commercially available permeation enhancer DMSO. Although Transdermal systems provide a promising route of delivery for new age drugs, conventional and new dosage forms are equally essential for other drugs to increase their therapeutic efficacy. The patented innovations of TDDS focus on these parameters to make dosage form more patients complied and site specific delivery of the drug. Moreover in vitro performance of the dosage form specifies the ultimate test for the therapeutic efficacy of the drug.

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