Formulation development and invitro evaluation of fentanyl patches for transdermal drug delivery system

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Abstract

Oral drug delivery system has various drawbacks like poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and frequent dosing, which can be both cost prohibitive and inconvenient. In present study transdermal drug delivery of Fentanyl was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Matrix type of transdermal patches were developed by using polymers Eudragit-L100, HPMC K4M and HPMC K15M. Transdermal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. Formulations were prepared with the varying concentrations polymers ranging from F1-F6, and all the formulations were evaluated for various physical parameters, *invitro* drug release studies by using dialysis membrane. Among all the formulations F6 formulation was found to be best and shown 96.97% drug release in 12 hours. For F6 formulation release kinetics was applied and it was observed that the formulation was following peppas mechanism of drug release. Drug excipients compatibility studies were carried out by using FT-IR and it was observed that they were no interactions.

Keywords: Fentanyl, Transdermal Patch, Solvent Casting Method, Dialysis Membrane, Release Kinetics, Compatibility Studies, FT-IR Studies.

Introduction

Fentanyl is an opioid analgesic. Fentanyl interacts predominately with the opioid mu-receptor but also binds to kappa and delta-type opioid receptors. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues. In clinical settings, Fentanyl exerts its principal pharmacologic effects on the central nervous system. Its primary actions of therapeutic value are analgesia and sedation. Fentanyl may increase the patient's tolerance for pain and decrease the perception of suffering, although the presence of the pain itself may still be recognized. In addition to analgesia, alterations in mood, euphoria and dysphasia, and drowsiness commonly occur. Fentanyl depresses the respiratory centers, depresses the cough reflex, and constricts the pupils. Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation(USP 25). Transdermal patch is a medicated adhesive pad that is designed to release the active ingredient at a constant rate over a period of several hours to days after application to the skin. It is also called skin patch. A transdermal patch uses a special membrane to control the rate at which the drug contained within the patch can pass through the skin and into the bloodstream. Drugs administered via skin patches include zolpidem tatrate, scopolamine, nicotine, estrogen, nitroglycerin, and lidocaine etc.[3,8,9]

Advantages: Transdermal drug delivery offers several important advantages over more traditional dosage forms. They avoid the first-pass effect, that is, the initial pass of drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes.

1. They provide extended therapy with a single application giving longer duration of action resulting in a reduction in dosing frequency, thus improving compliance over other dosage forms requiring more frequent dose administration.
2. They reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.
3. They are used for drugs with narrow therapeutic window.
4. They provide improved bioavailability and uniform plasma levels.

Disadvantages: Drugs undergoing metabolism during the passage through skin, such drugs cannot be administered by this system.

1. Drugs with very low or high partition coefficient fail to reach systemic circulation.
2. Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
3. Higher molecular weight candidates (>500Da) fail to penetrate the stratum corneum.
4. Propylene glycol and Tween80were selected as permeation enhancer and plasticizer.

Materials and Method

Fentanyl drug: Purdue pharma. HPMC K15M, HPMCK4M (HydroxyPropyl Methyl Cellulose): Cadila Pharma, Ahmedabad, India. Tween 80, Eudragit &L-

100: S.D. Fine chemical Pvt. Ltd, Mumbai, India. Potassium dihydrogen phosphate: Loba Chemie Pvt. Ltd, Mumbai. Sodium Hydroxide Pellets: Finar Chemicals Limited, Ahmedabad. Propylene glycol & Ethanol: Merck specialties Pvt. Ltd, Mumbai.

Preparation of Phosphate Buffer pH 7.4: Accurately measured 250 ml of 0.2 M potassium dihydrogen phosphate in a 1000 ml of volumetric flask and added 195.5 ml of 0.2 M sodium hydroxide and then water was added to make up the volume and adjusted pH 7.4 by using 0.2 M potassium dihydrogen phosphate/ sodium hydroxide.

***Construction of standard graph of Fentanyl*:** Standard graph of Fentanyl was plotted in PBS pH 7.4. Fentanyl was estimated λ_{max} by spectrophotometrically.

***Preparation of standard solution*:** Stock solution - I was prepared by dissolving Fentanyl 100 mg in 100 ml of methanol, so as to get a solution of 1 mg/ml concentration. T hen stock solution – II was prepared by taking 10 ml from the previous stock solution i.e. stock solution - I and dissolved in 100 ml of PBS pH 7.4, so as to get a solution of 100 µg/ml concentrations. Accurately measured aliquot portions of standard drug solution, from stock solution -II were taken, like 0.5 ml, 1 ml, 1.5 ml, 2 ml and2.5 ml were transferred in to 10 ml volumetric flasks and were diluted up to the mark with PBS pH 7.4. Absorbance of each solution was measured at λ_{max} of 255 nm against PBS pH 7.4 as the blank, by using UV-spectrophotometer. A graph was plotted by taking concentration of drug vs. absorbance was plotted& shown in Table 2 & Fig. 1.

Formulation

- ***Development of Transdermal patches*** **:** Transdermal drug delivery patches were prepared by solvent casting method.[1]
- ***Solvent casting method*:** Transdermal patches were prepared according to the formula shown in Table 08. Eudragit L100, HPMCK_4M and HPMCK15M were weighed in requisite ratios and they were then dissolved in dichloromethane and ethanol as solvent using magnetic stirrer. Fentanyl (36mg), Propylene glycol and Tween 80 were added to the above dispersion under continuous stirring. The uniform dispersion was poured in the petriplate. The rate of evaporation of solvent was controlled by inverting cut funnel over the patches. After 24h, the dried films were taken out and stored in desiccator. The formulations are shown in Table 1.

Evaluation

a. Evaluation of Transdermal patch by physical methods:[10,11,12]

- ***Physical appearance:*** All the Transdermal patches were visually inspected for color, clarity, flexibility & smoothness.
- ***Thickness:*** This thickness of the patches was assessed at 3 different points using screw gauze. For each formulation, three randomly selected patches were used.
- ***Weight variation:*** The three disks of 2x2 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.
- ***Flatness:*** Longitudinal strips were cut out from each patch, one the centre and two from either side. The length of each strip was measured and the variation in the length because of uniformity in flatness was measured by determining present constriction, considering 0% constriction equivalent to 100% flatness.
- ***Folding endurance:*** The folding endurance was measured manually for the preparation patch. A strip of the films (4x3 cm) was cut evenly and repeatedly folded at the same place till it is broken.
- ***Moisture uptake:*** The percent moisture absorption test was carried out to check the physical stability and integrity of the patch at high humid conditions. In the present study the moisture absorption capacities of the patch were determined in the following manner. The patches were placed in the desiccators containing 200 ml saturated solution of potassium chloride, to get the humidity inside the desiccators at 84% RH. After 3 days the films were taken and weighed the percentage moisture absorption of the patch was found**.**

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

- ***Moisture content:*** The patches were weighed individually and kept in a desiccators containing fused calcium chloride at 40 ºC for 24 h. The patches were reweighed until a constant weight was obtained. Moisture content was calculated in percentage based on the difference between the initial and the constant final weights of the patches.
- ***Swelling study:*** Completely dried membranes with a specified area (3.83 cm^2) were weighed and put in desiccators for 24 h. They were removed and exposed to relative humidity conditions of 75%(containing saturated solution of sodium chloride) in desiccators. Weight was taken on a single pan balance periodically until a constant weight was obtained. The swelling capacity of the membranes (in weight %) was calculated in terms of percentage increase in weight of membrane over the initial weight of the specimen. The experiments were carried out in triplicate and the average values were used for the calculation. The percentage degree of swelling (DS) was calculated as[5,6]

DS (%) = Ws-Wd/Wd× 100

Where, W_s and W_d indicate the weight of the swollen and dry membranes respectively.

- ***Drug content determination:*** The patch of area 3.83 cm^2 was cut and dissolved in PBS pH 7.4. Then solvent ethanol and dichloromethane, to make polymer soluble, were added to the mixture and the remaining volume was made up with PBS pH 7.4 to 100 ml in 100 ml volumetric flask. Then 1 ml was withdrawn from the solution and diluted to 10 ml. The absorbance of the solution was taken at 310 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.

b. **Evaluation of Transdermal patch by permeation studies:**

- ***Diffusion cell:*** Permeation studies were carried out on Franz diffusion cells. The Franz diffusion cell contains two compartments, the donor and receptor compartment. The receptor compartment is 5mm and holds a volume of 15 ml. The receptor compartment is attached to a collecting tube which allows easy collection of hourly sample while the process of diffusion. The donor and the receptor compartment are held together with help of a clap and the diffusion cell was placed on the magnetic stirrer while diffusion studies carried.
  The total area of the receptor compartment that is exposed to the Transdermal patch for diffusion is 3.83 cm^2.
- ***In vitro permeation studies using dialysis membrane*:** In vitro permeation of Fentanyl from Transdermal patches through dialysis membrane (Hi-Media) with molecular weight cut off of 12000 was studied. The membrane was mounted over a Franz diffusion cell and a Transdermal patch. The receiver compartment of the diffusion cell was filled with 15.0 ml of PBS pH 7.4 and the setup was placed over a magnetic stirrer with temperature maintained at 37^0C. Samples of 3 ml were withdrawn and replenished immediately from the receiver compartment at 1, 2, 3, 4, 6 and 12h. They were stored in refrigerated condition till the analysis was performed. The content of Fentanyl in the samples was analyzed by UV-Visible spectrophotometer. The concentrations of drug were determined at 266 nm.[2,7]

Kinetic modeling of drug release:

Mechanism of drug release: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

A. ***Zero order release model:*** To study the zero–order release kinetics the release rate data are fitted to the following equation.

$Q = K_{0\,t}$

Where, Q= amount of drug released at time t

K_0=zero order release rate constant

The plot of % drug release versus time is linear.

B. ***First order release model:*** The release rate data are fitted to the following equation

$\ln (100-Q) = \ln 100 - k_1 t$

Where, Q= percent drug release at time t

K_1= first order release rate constant

The plot of log % drug release versus time is linear.

C. ***Higuchi's Release Model:*** To study the Higuchi release kinetics, the release rate data were fitted to the following equation

$Q = K_H t^{1/2}$

Where, Q= percent drug release at time t

K_H= Higuchi's (diffusion) rate constant

In Higuchi's model, a plot of % drug release versus square root of time is linear.

D. ***Korsmeyer-peppas release model:*** The release rate data were fitted to the following equation

$F = (M_t/M) = K_m t^n$

Where, M_t= drug release at time t

M= total amount of drug in dosage form

F= fraction of drug release at time t

K_m=constant dependent on geometry of dosage form

n=diffusion exponent indicating the mechanism of drug release.

If n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or non-fickian diffusion (Swellable & Cylindrical Matrix).In this model, a plot of log (M_t/M) versus log (time) is linear.

Drug excipients interaction studies

FTIR spectrum interpretation: IR spectral analysis was carried out using FT-IR by the KBr disc method. The sample and KBr were triturated and compressed to get the discs. The samples of pure drug, dummy formulation and optimized formulation (F-7) were analyzed between wave numbers 4000.0 and 400.0 cm^{-1}.

Results and Discussion

FTIR Studies: FTIR of pure drug shown in Fig. 2 & optimized formulation was shown in Fig. 3.

Evaluation of Fentanyl Transdermal patches: Evaluations tests are shown in Table 3.

Physical appearance: All the Transdermal patches were visually inspected for colour, clarity, flexibility.

Flatness: All the Transdermal patches were found to be flat without any foam.

The prepared Fentanyl Transdermal patches were evaluated by physical methods such as Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake and Moisture content and all the results were found to be within the pharmacopeial limits. Evaluation of Transdermal patch by *In-vitro* permeation studies using dialysis membrane are shown in Table 4 & Fig. 4.

The prepared Fentanyl Transdermal patches were evaluated for In-vitro permeation studies using dialysis

membrane, among all the 12 formulations F6 formulation which contain HPMC K4M 200mg had shown 96.97% cumulative drug release within 12 hours. And compared to HPMC K15M, HPMC K4M showed better drug release profile. Kinetics of *In-vitro* permeation studies using dialysis membrane are shown in Table 5 & Fig. 5. The kinetics of *In-vitro* permeation studies using dialysis membrane for F6 formulation was plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.9892. And the n value was found to be 0.6203 which indicates the drug release pattern was found to be non-Fickian diffusion.

Table 1: Formulations of Fentanyl Transdermal Patch

S. No	Ingredients	F1	F2	F3	F4	F5	F6
1	Drug(mg)	100	100	100	100	100	100
2	Eudragit-L100(mg)	100	150	-	-	-	-
3	$HPMCk_4M$(mg)	-	-	100	150	-	-
4	$HPMCk_{15}M$(mg)	-	-	-	-	100	150
5	Dichloromethane(ml)	8	8	8	8	8	8
6	Ethanol(ml)	8	8	8	8	8	8
7	Propylene glycol(ml)	1.2	1.2	1.2	1.2	1.2	1.2
8	Tween-80(ml)	1.2	1.2	1.2	1.2	1.2	1.2

Table 2: Standard graph of Fentanyl

Concentration (µg/ml)	Absorbance(nm)
5	0.123
10	0.210
15	0.320
20	0.411
25	0.501

Table 3: Evaluation of Transdermal patch by physical methods

Formulation	Thickness (mm)	Folding endurance	Drug content (%)	Moisture uptake (%)	Moisture content (%)
F1	0.3569	20	45	7.98	3.77
F2	0.3520	25	65	25.05	9.2
F3	0.3470	27	57.5	13.09	5.16
F4	0.3496	24	60	15.63	5.66
F5	0.3460	30	67.5	11.73	4.87
F6	0.3517	32	92.5	19.65	12.67

Table 4: Evaluation of Transdermal patch by *In-vitro* permeation studies using dialysis membrane

Time (hrs)	% Drug release					
	F1	F2	F3	F4	F5	F6
0.5	4.55	7.45	3.54	5.44	5.32	10.44
1	10.05	15.1	10.1	9.49	10.9	19.55
2	15.3	19.8	12.8	11.3	19.6	30.32
4	19.6	28.3	25.5	25.6	24.9	42.8
6	26.9	34.1	30.9	32.3	31.2	53.5
8	33.56	41.1	40.4	39.9	38.0	66.3
10	45.66	50.1	54.5	56.3	50.3	82.0
12	55.33	65.8	77.7	87.4	67.9	96.97

Table 5: Kinetics of *In-vitro* permeation studies using dialysis membrane

Cumulative (%) release Q	Time (T)	Root (T)	Log (%) release	Log (T)	Log (%) remain	Release rate (cumulative % release/t)	1/cum% release	Peppas log Q/100	% drug remain	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
10.44	0.5	0	0.897	0.000	2.000	10.132	0.0043	-0.356	100	4.642	4.642	0.000
19.55	1	1.000	1.306	0.000	1.902	20.236	0.0494	-0.694	79.7644	4.642	4.305	0.337
30.32	2	1.414	1.444	0.301	1.858	13.904	0.0360	-0.556	72.19241	4.642	4.164	0.478
42.8	4	2.000	1.632	0.602	1.757	10.720	0.0233	-0.368	57.12042	4.642	3.851	0.790

53.5	6	2.449	1.729	0.778	1.667	8.932	0.0187	-0.271	46.40707	4.462	3.594	1.048
66.3	8	2.828	1.822	0.903	1.527	8.298	0.0151	-0.178	33.61257	4.642	3.227	1.414
82.0	10	3.162	1.914	1.000	1.253	8.209	0.0122	-0.086	17.9123	4.642	2.616	2.025
96.97	12	3.464	1.976	1.079	0.724	7.892	0.0106	-0.024	5.294503	4.642	1.743	2.899

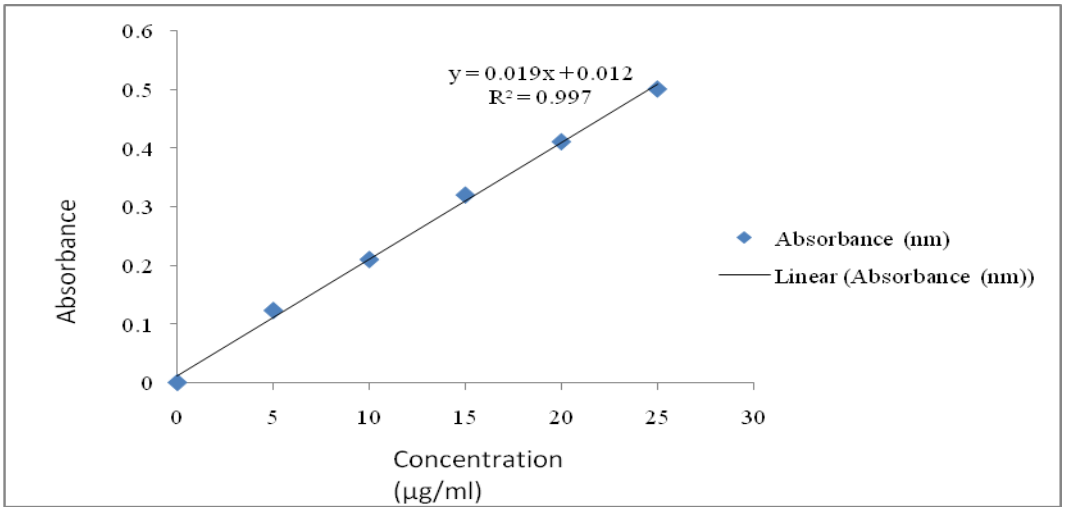

Fig. 1: Standard curve of Fentanyl

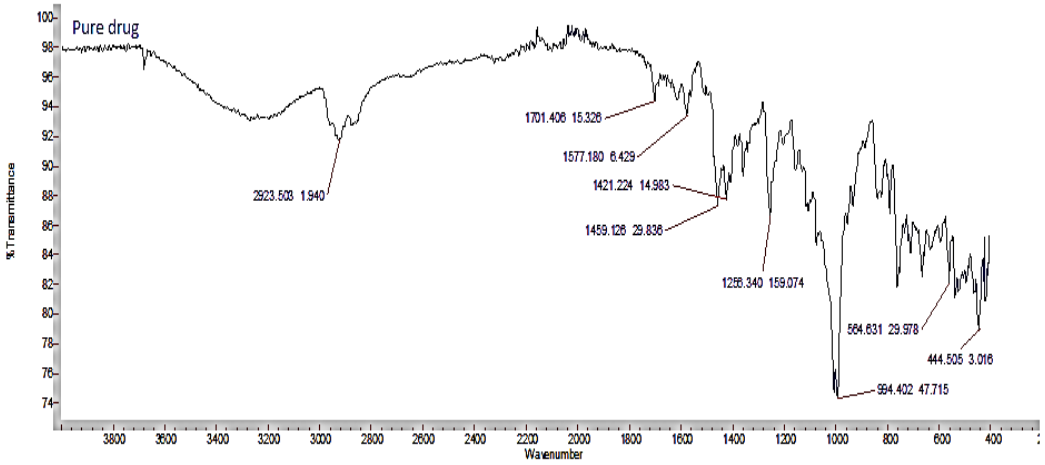

Fig. 2: FTIR of pure drug

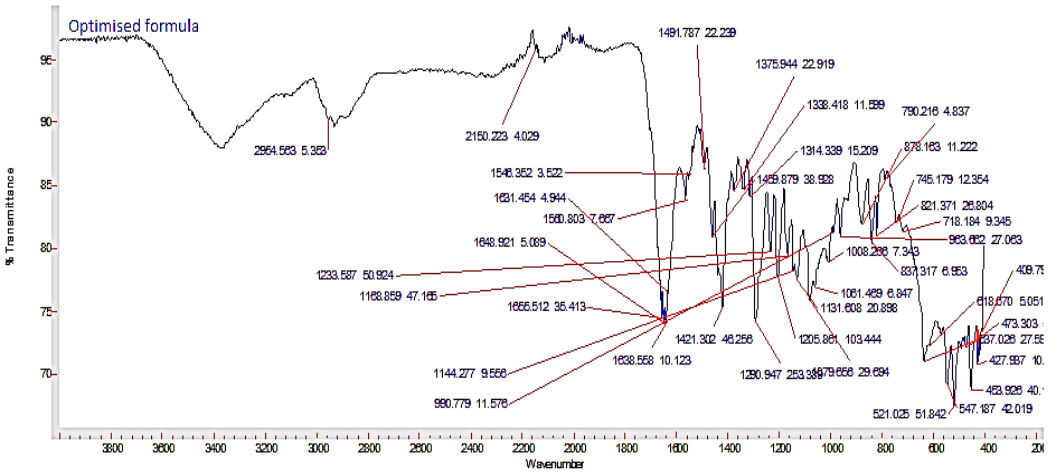

Fig. 3: FTIR of Optimised formulation

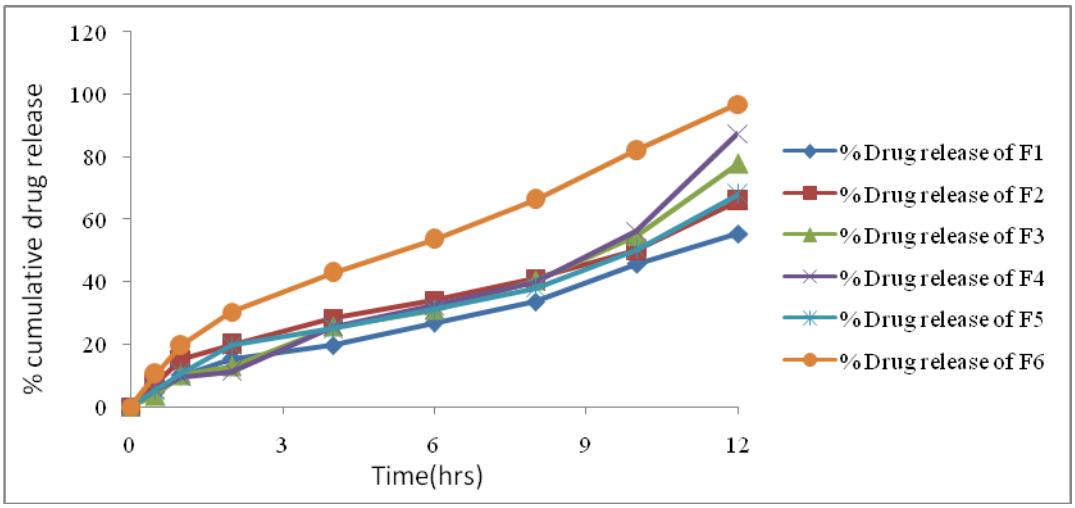

Fig. 4: Release profile of *In-vitro* permeation studies using dialysis membrane

Conclusion

In present study transdermal drug delivery of Fentanyl was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Oral drug delivery system has various drawbacks like poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. Matrix type of transdermal patches was developed by using polymers Eudragit-L100, $HPMCK_4M$ and HPMCK15M. Transdermal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. Drug excipients compatibility studies were carried out by using FTIR, and it was observed that there were no interactions.

Formulations were prepared with the varying concentrations polymers ranging from F1-F6, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be were found to be within the pharmacopeia limits, *invitro* drug release studies by using dialysis membrane. Among all the 12 formulations F6 formulation which contain HPMC K4M 150mg had shown 96.97% cumulative drug release within 12 hours. And compared to HPMC K15M, HPMC K4M showed better drug release profile. For F6 formulation release kinetics were plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.9892. The n value was found to be 0.6203 which indicates the drug release pattern was found to be non-Fickian diffusion.

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