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DESIGN AND CHARACTERISATION OF TRANSDERMAL FILM OF GLICLAZIDE FOR THE TYPE-II DIABETES

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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/or frequent dosing, which can be both cost prohibitive and inconvenient. In present study transdermal drug delivery of Gliclazide was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Matrix type of transdermal films were developed by using polymers Eudragit-S100, HPMCk$_4$M and HPMCk15M.Transdermal films were prepared by employing solvent casting method. Propylene glycol was selected as permeation enhancer and plasticizer. Formulations were prepared with the varying concentrations polymers ranging from F1-F12, and all the formulations were evaluated for various physical parameters, invitro drug release studies by using dialysis membrane. Among all the formulations F5 formulation was found to be best and shown 94.7% drug release in 12 hours. For F5 formulation release kinetics were applied and it was observed that the formulation was following peppas mechanism of drug release. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that they were no interactions.

Keywords: *Gliclazide, Transdermal film, Eudragit-S100, HPMCk$_4$M and HPMCk15M.*

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INTRODUCTION:

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.

Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. Is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered in this method.

The first transdermal patch was approved by the FDA in 1979. It was a patch for the treatment of motion sickness. In the mid-1980s, the pharmaceutical companies started the development of a nicotine patch to help smokers quit smoking, and within a few months at the end of 1991 and beginning of 1992 the FDA approved four nicotine patches. The idea of delivering drugs through skin is old, as the use is reported back in16th century B.C. The husk of castor oil plant in water was placed on an aching head. Today the transdermal drug delivery is well accepted for

delivering drug to systemic circulation. Until recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven effective delivered through the skin — typically cardiac drugs such as nitroglycerin and hormones such as estrogen.

Today drugs administered through skin patches include scopolamine (for motion sickness), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina) and lidocaine to relieve the pain of shingles (herpes zoster). Non-medicated patches include thermal and cold patches, weight loss patches, nutrient patches, Skin care patches (therapeutic and cosmetic) and aroma patches and patches that measure sunlight exposure.

MATERIALS & METHODS:

Materials: Gliclazide, Distilled water, Ethanol, Eudragit S-100, $HPMCk_{15}M$, $HPMCk_4M$, Methanol, $HPMCk_{100}M$,

Potassium dihydrogen phosphate, Sodium hydroxide pellets.

Method: Transdermal drug delivery films were prepared by solvent casting method. 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. Gliclazide (36mg), Propylene glycol and Tween 80 was added to the above dispersion under continuous stirring. The uniform dispersion was poured in the Petri plate. The rate of evaporation of solvent was controlled by inverting cut funnel over the films. After 24h, the dried films were taken out and stored in desiccators.

Table: 1 Formulations of Gliclazide Transdermal Film

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Drug(mg)	200	200	200	200	200	200	200	200	200	200	200	200
2	Eudragit-L100(mg)	-	-	-	-	-	-	-	-	-	-	-	-
3	Eudragit S100(mg)	-	-	200	-	-	-	-	-	-	-	200	400
4	$HPMCk_4M$(mg)	-	-	-	-	-	-	-	-	-	300	-	-
5	Ethyl cellulose	150	-	-	-	-	200	200	-	-	-	-	-
6	$HPMCk_{15}M$(mg)	-	300	400	-	300	-	-	-	-	-	-	-
7	$HPMCk_{100}M$(mg)	-	-	-	-	400	-	300	-	-	-	-	-
8	HPMC E50(mg)	-	-	-	-	-	-	-	200	300	-	-	-
9	Methanol (ml)	-	-	-	-	-	-	5	-	-	-	-	-
10	Ethanol(ml)	-	-	-	-	-	-	-	-	-	-	5	5
11	Propylene glycol(ml)	-	-	20	40	40	40	40	-	-	-	20	20
12	Dimethyl	-	-	-	-	-	-	-	-	-	-	5	5
13	Water (ml)	5	5	15	15	15	15	15	5	5	5	-	-
14	Chloroform(ml)	2	2	-	-	-	-	-	2	2	-	-	-

Evaluation of Transdermal film by physical methods:

- **Physical appearance*:*** All the Transdermal films were visually inspected for color, clarity, flexibility & smoothness.
- **Thickness:** This thickness of the films was assessed at 3 different points using screw gauze. For each formulation, three randomly selected films 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 film, 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 film. 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 film at high humid conditions. In the present study the moisture absorption capacities of the film were determined in the following manner. The films 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 film was found.

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

- **Moisture content:** The films were weighed individually and kept in a desiccators containing fused calcium chloride at 40 ºC for 24 h. The films 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 films.
- **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

$$DS\ (\%) = Ws- \ Wd/Wd \times 100$$

Where, W_s and W_d indicate the weight of the swollen and dry membranes respectively[46].

- **Drug content determination:** The film 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 221 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.

Evaluation of Trandermal film 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 film for diffusion is 3.83 cm^2.

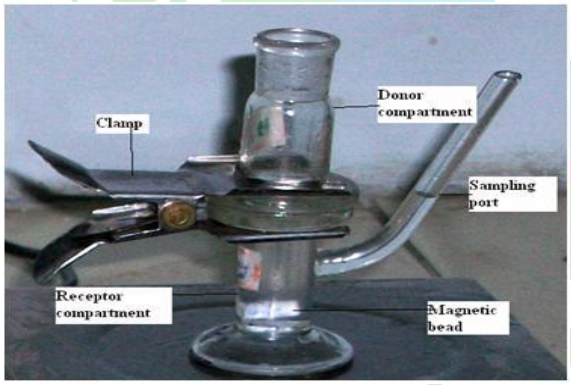

Fig. 1: Franz diffusion cell

- **In vitro permeation studies using dialysis membrane:** In vitro permeation of Gliclazide from Transdermal films 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 film. 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 Gliclazide in the samples was analyzed by UV-Visible spectrophotometer.

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.

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.

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

$$\ln (100\text{-}Q) = \ln 100 - k_1 t$$

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.

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.

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: FT-IR 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 were analyzed between wave numbers 4000.0 and 400.0 cm^{-1}.

RESULTS AND DISCUSSION:

Evaluation of Gliclazide Transdermal films:

Physical appearance: All the Transdermal films were visually inspected for color, clarity, flexibility.

Flatness: All the Transdermal films was found to be flat without any foams

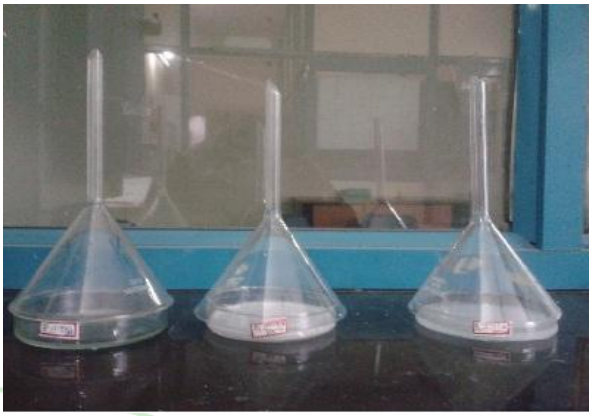

Fig 2: solvent casting method

Table 2: 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
F7	0.3478	40	101.7	9.42	3.43
F8	0.3437	37	85	10.87	4.72
F9	0.3503	34	55	16.44	6.62
F10	0.3532	29	62.5	13.08	6.17
F11	0.3546	26	85	20.63	7.94
F12	0.3503	31	82.5	15.73	6.55

The prepared Gliclazide Transdermal films 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.

Table: 3 Evaluation of Trandermal patch by In-vitro permeation studies using dialysis membrane

Time (hrs)		% Drug release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	9.05	15.1	10.1	9.49	20.2	10.9	17.5	12.0	11.1	12.7	10.0	20.4
2	13.3	19.8	12.8	11.3	27.8	19.6	21.9	17.5	13.0	17.9	12.5	25.4
4	14.6	28.3	21.5	22.6	42.8	24.9	33.5	23.4	23.3	27.4	23.6	33.0
6	21.9	34.1	25.9	32.3	53.5	31.2	40.0	30.9	33.4	32.7	30.9	41.7
8	32.7	41.1	33.4	43.9	66.3	38.0	46.5	48.1	52.7	50.6	36.7	47.9
10	40.4	50.1	44.5	56.3	82.0	50.3	64.2	60.0	66.4	63.0	45.9	63.0
12	54.2	65.8	56.7	69.4	94.7	65.9	91.9	78.7	79.1	74.8	56	80.9

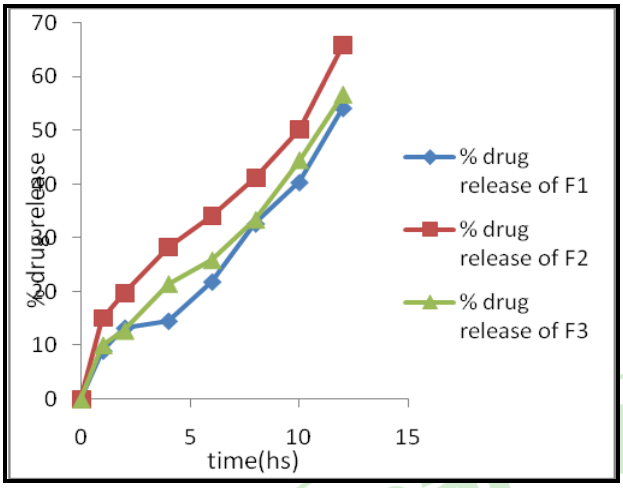

Fig 3 : Percentage drug release of formulation F1-F3

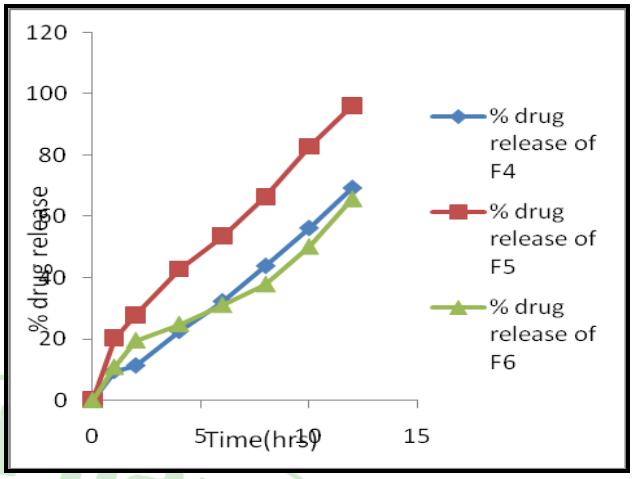

Fig 4 : Percentage drug release of formulation F5-F6

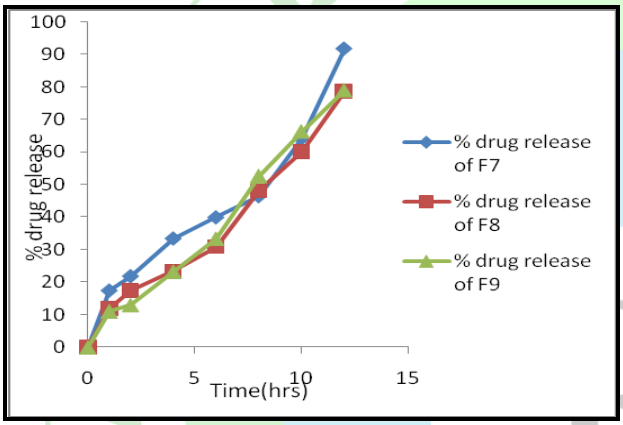

Fig 5 : Percentage drug release of formulation F7-F9

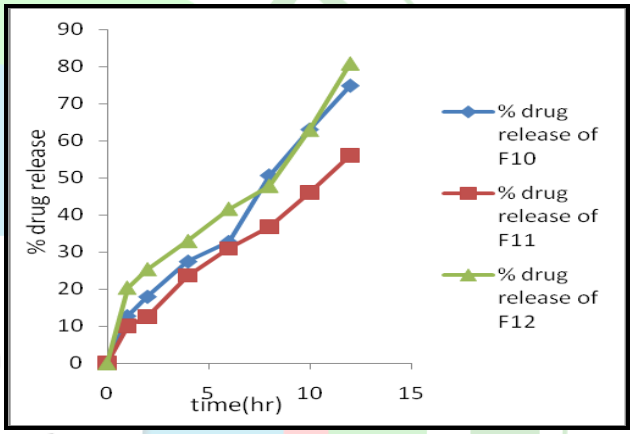

Fig 6 : Percentage drug release of formulation F10-F12

The prepared Gliclazide Transdermal films were evaluated for In-vitro permeation studies using dialysis membrane, among all the 12 formulations F5 formulation which contain HPMC K100M 400mg had shown 94% cumulative drug release within 12 hours. And compared to HPMC K15M, HPMC K4M, Eudragit S100, HPMC E50, Ethyl cellulose showed better drug release profile.

Table: 4 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)
0	0	0			2.000	
20.2356	1	1.000	1.306	0.000	1.902	20.236
27.80759	2	1.414	1.444	0.301	1.858	
42.87958	4	2.000	1.632	0.602	1.757	10.720
53.59293	6	2.449	1.729	0.778	1.667	8.932
66.38743	8	2.828	1.822	0.903	1.527	8.298
82.0877	10	3.162	1.914	1.000	1.253	8.209
94.7055	12	3.464	1.976	1.079	0.724	7.892

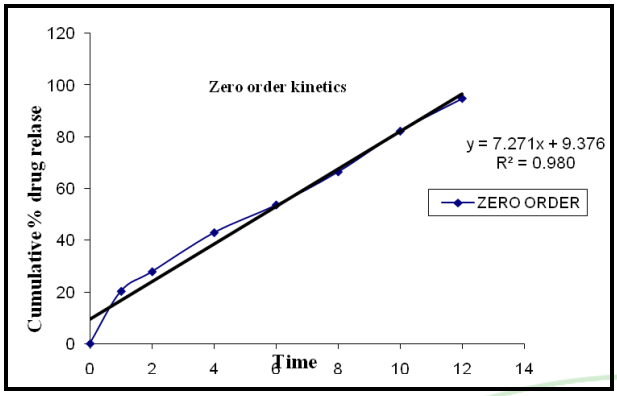

Fig 7 : Zero order kinetics

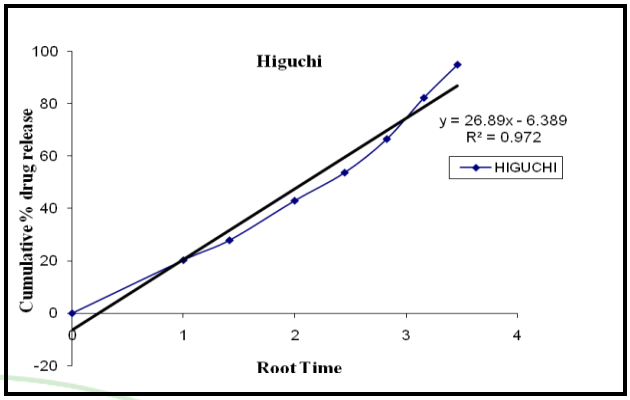

Fig 8: Higuchi plot

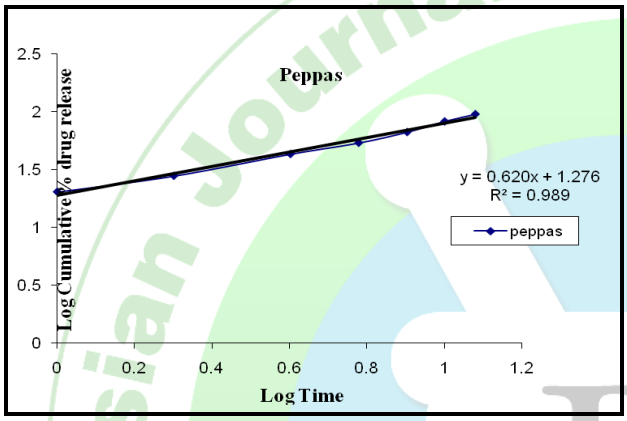

Fig 9: Peppas plot

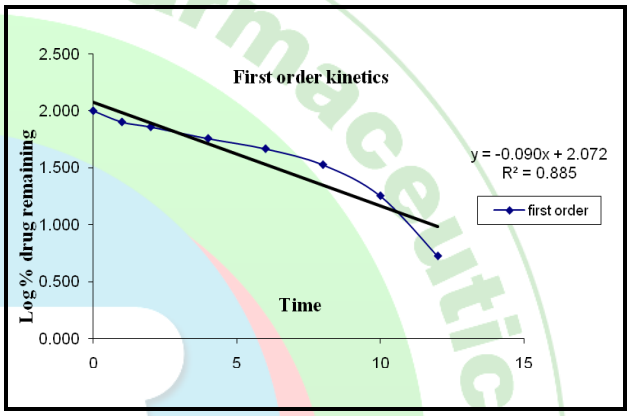

Fig 10 : First order kinetics

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.

CONCLUSION:

In present study transdermal drug delivery of Gliclazide 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 films was developed by using polymers Eudragit-L100, HPMCk_4M and HPMCk15M. Transdermal films were prepared by employing solvent casting method. Propylene glycol was selected as permeation enhancer and plasticizer. Drug excipient 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-F12, 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 pharmacopeial limits, invitro drug release studies by using dialysis membrane. Among all the 12 formulations F5 formulation which contain HPMC K4M 400mg had shown 94% 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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