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Pharmaceutical Sciences **Research Article……!!!**

FORMULATION AND EVALUATION OFTRANSDERMAL PATCH CONTANING ANTIHYPERTENSIVE DRUG

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KEYWORDS:

Transdermal drug delivery, Felodipine, HPMC,Eudragit.

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ABSTRACT

The objective of the present study is to develop the matrix type of transdermal patch of Felodipine to avoid first pass metabolism, using Hydroxy propyl methyl cellulose (HPMC) Eudragit RS 100 and ethyl cellulose (EC) with PEG 400 (as plasticizer) and propylene glycol (as penetration enhancer). The solvent casting technique was employed for the preparation of Felodipine transdermal patches. The dry films were evaluated for weight variation, thickness uniformity, moisture content, moisture uptake, folding endurance and % drug content. *In-vitro* release studies were performed using Franz's diffusion cell and permeation studies were carried out by using rat skin. The concentration of diffused drug was measured using UV- visible spectrophotometer at λ max 362 nm. IR studies revealed that the drug and polymer were compatible with each other and all the batches prepared and evaluated, F2,F4 and F7 showed promising results. It was concluded that HPMC and ethyl cellulose are useful in formulating sustained release patches.

INTRODUCTION:

TRANSDERMAL DRUG DELIVERY SYSTEMS (TDDS)

Transdermal drug delivery systems (TDDS), also known as patches, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus, various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc have been emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug.

PATHWAYS OF DRUG ABSORPTION THROUGH THE SKIN:

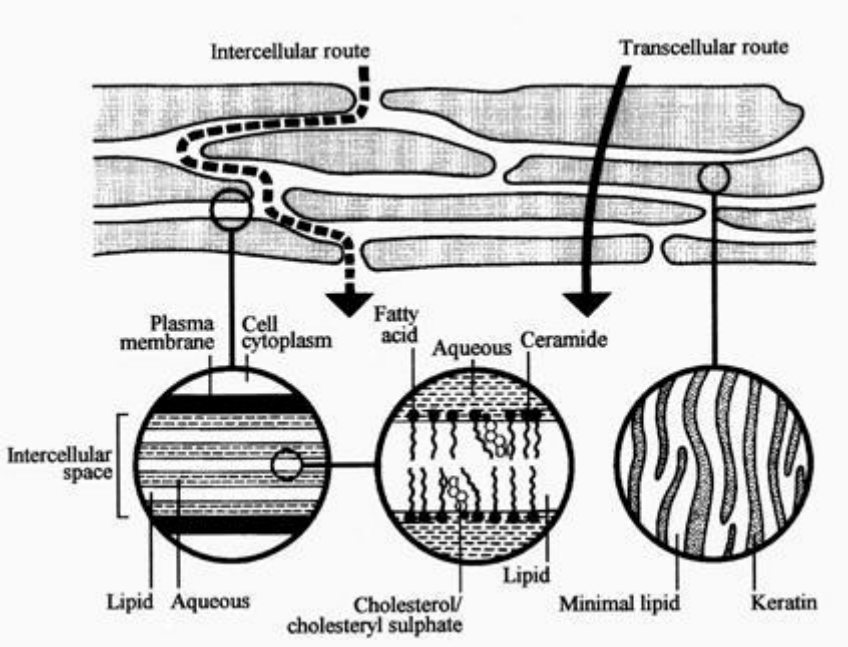


Figure No.1:Transport of drugs through stratum corneum

The drug can be absorbed by various pathways through the skin depending on the physicochemical properties of the drug. Both lipophilic and hydrophilic drugs are absorbed from different routes. The upper stratum corneum of the skin opposes the absorption of drug but presence of various absorption routes facilitates the entry of drug and transport of drug to the systemic circulation. Various drug absorption routes are as follows:

a) Transfollicular route

Transfollicular route is the shortest pathway that drug has to follow to reach the systemic circulation that provides a large area for diffusion of drugs. Skin has various sweat glands, oil glands, hair follicles and pores opening to the outer surface of the skin via their ducts. These ducts offer a continuous channel across the stratum corneum for drug transport but various factors like secretion from glands, content and amount of secretion etc., affect the transport of drugs through this route. However, trans appendageal route occupies only 0.1% of total skin surface and therefore contributes a little.

b) Transcellular route

Drug delivering through this route passes from corneocytes which has highly hydrated keratin creating hydrophilic pathway. Corneocytes are surrounded by lipids connecting these cells. So a drug requires a number of partitioning and diffusion steps. It is the most widely used route by various types of drugs. In transcellular route drug passes through the matrix (cytoplasm) of the cells. This route is suitable for hydrophilic drugs. The drug passes through the corneocytes of stratum corneum. The highly hydrated keratin provides aqueous pathway to the hydrophilic drugs. A number of partitioning and diffusion steps are needed to pass the drug through the cell matrix.

c) Intercellular route

As name indicates in intercellular pathway the drug diffuses through the continuous lipid matrix present between the cells. The barrier property of this route is due tortuous structure formed by corneocytes and the drug has to pass through the alternating lipid and aqueous domain by partitioning into the lipid bilayer and diffusing to the inner side. It has been found that water has to travel 50 times more by this route so; it is suitable mainly for uncharged lipophilic drugs.

Percutaneous absorption of drug molecules is of particular importance in the case of transdermal drug delivery systems because the drug has to be absorbed to an adequate extent and rate to achieve and maintain uniform, systemic, therapeutic levels throughout the duration of use. In general, once drug molecules cross the stratum corneal barrier, passage into deeper dermal layers and systemic uptake occurs relatively quickly and easily.

MATERIALS: Felodipine was the gift sample Astra Zeneca Bangalore, HPMC Ethyl cellulose,Eurdragit ,pvp and PEG was obtained from laboratory grade.

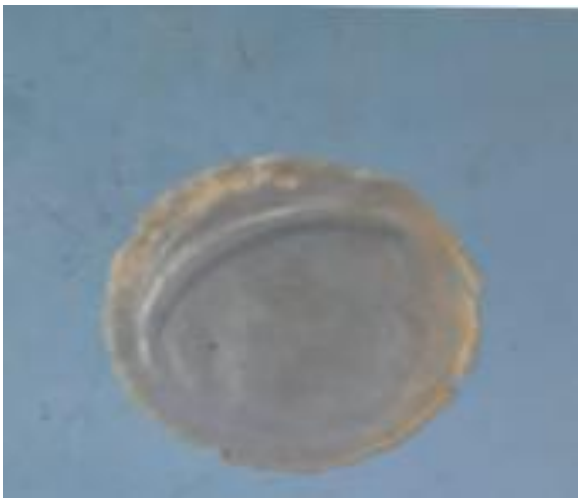
Method of preparation of Transdermal patches: .Transdermal patches of Felodipine were prepared by solvent casting technique. Solution of PVP with EC,HPMC,and Eudragit RS 100 were dissolved in 20 ml mixture of methanol and chloroform in the ratio 1:1 as per the formulation table. PEG 400 and propylene glycol added in required amounts as per formulation chart to the prepared solution and stirred well. The accurately weighed drug was mixed with the above mixture and mixed well to obtain homogenous mixture.

After proper mixing the solution was kept for stabilization and complete removal of air bubbles. Then the above mixture was casted in a glass mould of 9 cm^2 previously coated with thin layer of glycerine to prevent the adhesion of formed patch to the mould. The rate of evaporation was controlled by inverting a glass funnel over the glass mould. The mould was kept a side for drying at room temperature for 24 hrs. After 24 hrs the dried films was carefully removed from the mould and stored in a desiccator.

Table no 1:Composition of Felodipine transdermal patches

Formulation code	Drug (mg)	HPMCK 100 (mg)	EC (mg)	Eurdragit RS100(mg)	PVP (mg)	PEG400 (ml)	Solvent methanol and chloroform 1:1(ml)
F1	**80**	**125**	**----**	**175**	**20**	**15**	**20**
F2	**80**	**125**	**175**	**-----**	**20**	**15**	**20**
F3	**80**	**---**	**125**	**175**	**20**	**15**	**20**
F4	**80**	**150**	**150**	**-----**	**20**	**15**	**20**
F5	**80**	**150**	**----**	**150**	**20**	**15**	**20**
F6	**80**	**-----**	**150**	**150**	**20**	**15**	**20**
F7	**80**	**200**	**100**	**------**	**20**	**15**	**20**
F8	**80**	**200**	**-------**	**100**	**20**	**15**	**20**
F9	**80**	**----**	**200**	**100**	**20**	**15**	**20**

FIGURE 2: FELODIPINE PATCH



EVALUATION OF PATCHES

Preparation of the standard calibration curves of Felodipine

Standard calibration curves of Felodipine was prepared in pH 7.4 buffer and volume was made up to 100ml in volumetric flask using pH 7.4 PBS. From this stock solution aliquots of 2.5, 5, 7.5, 10, 12.5 and 15ml were withdrawn and diluted up to 50ml in volumetric flask to give concentration of 5, 10, 15, 20, 25 and 30µg/ml. Absorption of each solution was measured at 362 nm using double beam UV spectrophotometer and pH 7.4 buffer as a reference standard.

DRUG-EXCIPIENT COMPATIBILITY STUDIES

Fourier Transform Infrared (FTIR) Spectroscopy

Potential chemical interaction between drug and polymer may change the therapeutic efficacy of the drug. To investigate the possibility of chemical interaction between drug and polymer FTIR spectra of pure Felodipine and polymers used in formulations were analysed over the range 400–4000 cm^{-1}.

Thickness:

Thickness of the transdermal patch is measured by screw gauze at three different points of the patch and average of the three is taken as thickness of the patch a uniformly thick patch will have an equal thickness at every point. The variation of thickness within the patch and patch to patch can be calculated.

Folding endurance:

Folding endurance is calculated by continuously folding the strip of the patch /film of a specific area at the same place until it breaks or folded up to 300 times. The number of times of folding the patch without breaking gives the folding endurance of the patch. The folding endurance determines the flexibility of the patch.

Drug content determination:

An accurately weighed portion of film (about 80 mg) is dissolved in 100 ml of phosphate buffer of pH 7.4 and then the solution is shaken continuously for 24 h in shaker . Then the whole solution was sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Weight variation:

This was done by weighing three different patches of individual batch taking the uniform size (3cm * 3cm) at random and calculating the average weight of 3.The tests was performed on films which were dried at 60^{o}C for 4 hrs prior to testing.

Moisture content:

The prepared films are weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.

% Moisture content = Initial weight – Final weight X 100

Moisture Uptake:

Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below. **% moisture uptake = Final weight – Initial weight X 100**

Stabilitystudies:

Stability study was conducted to determine the time period for which the patch remains viable and usable. In unstable patch formulations drug starts degrading gradually so stability is tested according to ICH guidelines at 40^{0}C/75% RH for 6 months. Samples are taken at 0, 30, 60, 90 and 180 days and tested for its stability.

***In vitro* Drug permeation studies:**

a) *In-vitro* drug release studies:

The *in vitro* release study was carried out using modified diffusion assembly. The transdermal patch ($3*3cm^{2}$) was adhered to the cellulose acetate membrane and tied firmly to the diffusion tube. This assembly was lowered in a beaker containing 100 ml of PBS so that the membrane assembly just touches the solution in the beaker .The whole assembly was kept on a magnetic stirrer and study was conducted at a temperature of 37 ± 2°C.The contents in the beaker were stirred using a Teflon bead at a constant speed. Samples of 5 ml were collected at predetermined time and replenished with fresh

prewarmed medium. Drug content in the samples was estimated using UV/visible spectrophotometer at 362nm.Cumulative percentage of the released drug was calculated and plotted against time.

b) ***In vitro*** **Skin Permeation studies:**

Modified Franz diffusion cell with a inner diameter of 5cm^2 was used for *In vitro* permeation studies. A full thickness of Albino rat skin was excised from dorsal site and washed with water. The fatty tissue layer was removed by using surgical scissors. The outer portion with hairs was applied with depilatory and allowed to dry. With the help of wet cotton the hairs were scrubbed and washed with normal saline solution. The skin was kept in normal saline solution and allowed to equilibrate At room temperature prior to diffusion study. The skin was mounted between donor and receptor compartment of cell and clamped in such a way that the dermal side (inner side) will be in contact with receptor medium.

The stratum corneum side of the skin was kept in intimate contact with the transdermal patch under the test.The receptor compartment was with 100 ml of PBS of pH 7.4.The whole assembly was kept on a magnetic stirrer and study was conducted at 37 ± 2°C.The amount of the permeated drug was determined by removing 5 ml at pre-determined time and replenishing with an equal volume of fresh medium. The samples were analysed for drug content using UV spectrophotometer at 362 nm.

RESULTS & DISCUSSION:

Figure No 3:Absorption spectra of Felodipine in PBS 7.4

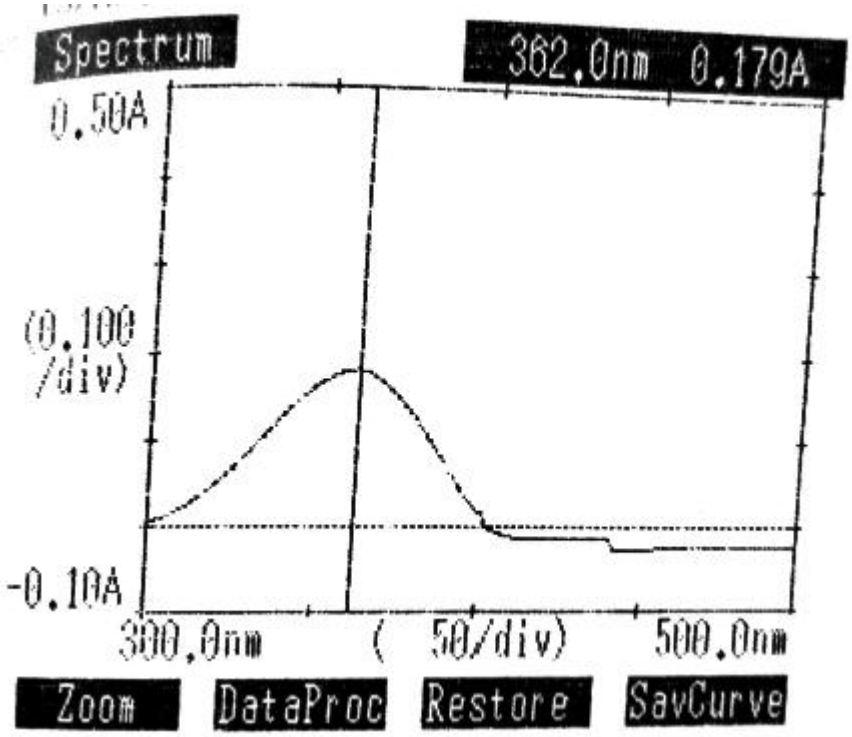


Figure No 4:Standard plot of Felodipine in PBS 7.4

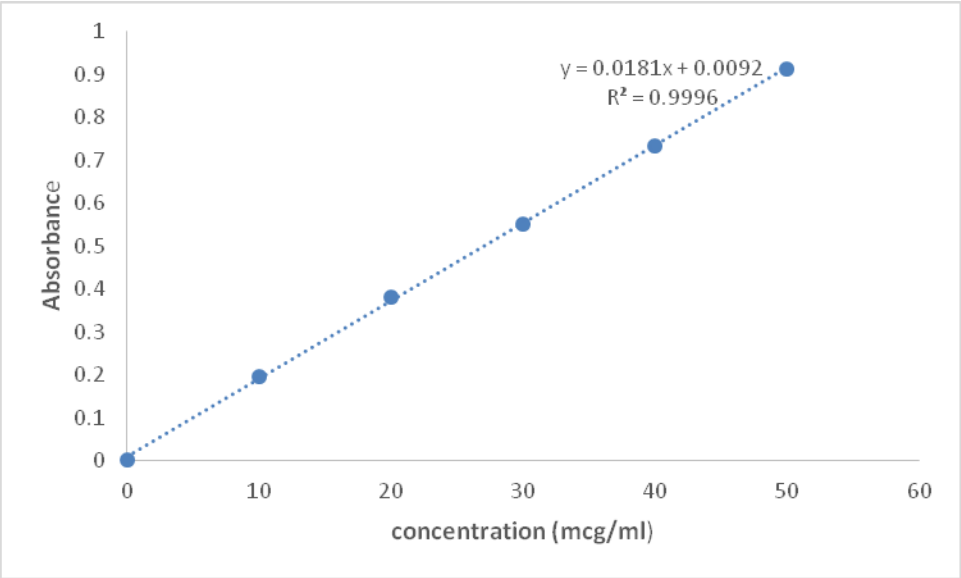


Figure No 5:FTIR of Felodipine

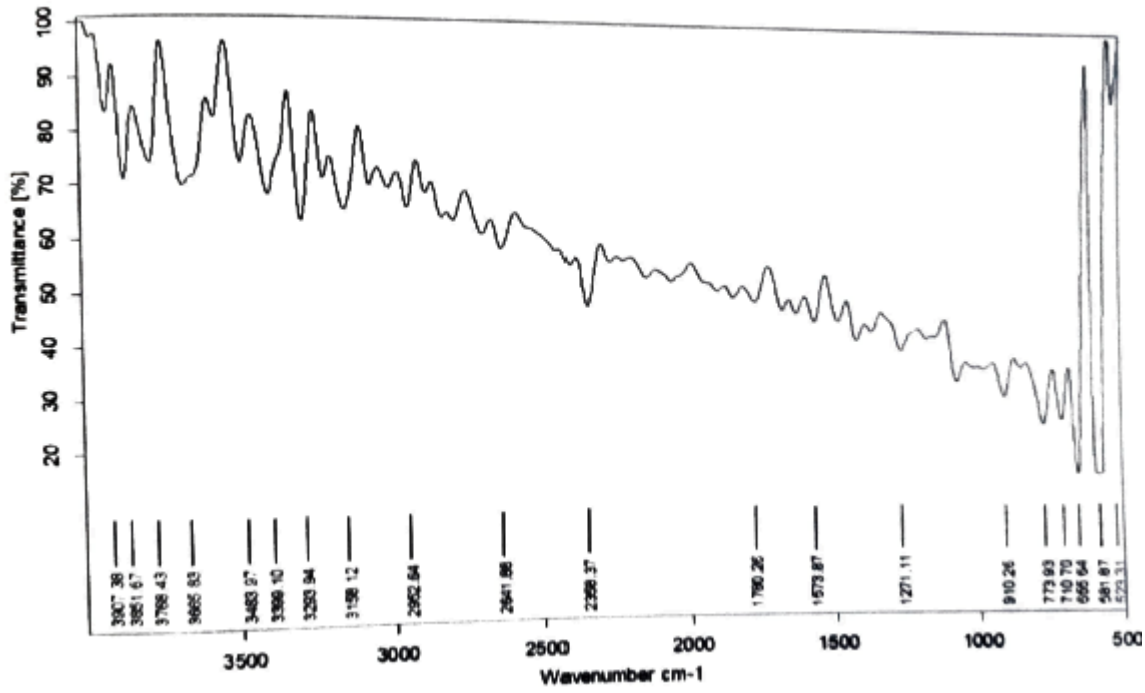


Figure No 6:FTIR of Felodipine with polymers used in formulations

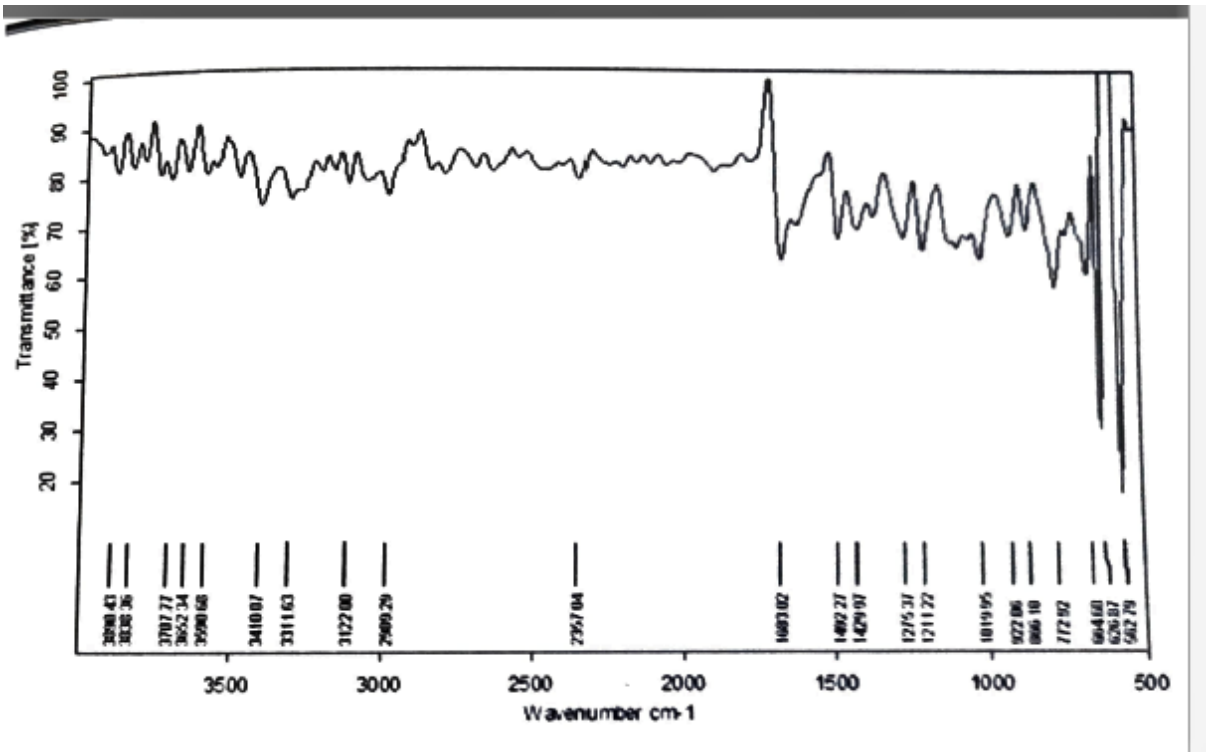


Table No 2:Physicochemical evaluation Felodipine transdermal patches

Formulation code	Thickness	Folding endurance	Weight variation	% Drug Content	%Moisture uptake	%Moisture content
F1	0.14±0.028	195±5.2	0.011±0.003	90.4±4.02	4.12	2.41
F2	0.15±0.019	186±3.2	0.013±0.002	98.9±3.32	4.19	3.12
F3	0.12±0.018	179±7.3	0.014±0.016	90.1±5.22	5.29	3.29
F4	0.15±0.021	189±3.9	0.012±0.003	98.4±4.13	5.14	3.08
F5	0.14±0.023	181±5.5	0.015±0.004	91.12±5.91	4.18	2.78
F6	0.12±0.016	179±4.1	0.014±0.010	90.1±3.51	3.18	2.74
F7	0.11±0.026	197±7.6	0.013±0.005	98.2±2.99	4.12	3.45
F8	0.16±0.031	189±4.1	0.012±0.008	90.2±2.99	3.58	2.17
F9	0.14±0.018	190±7.6	0.013±0.006	91.2±2.99	5.22	2.04

Table No 3: *In-vitro* release profile of Felodipine transdermal patches from F1 to F3

Time (hr)	F1	F2	F3
0	0	0	0
1	16.25±0.46	10.73±0.57	9.89±0.29
2	26.41±0.38	14.25±0.28	12.23±0.92
3	35.42±0.36	21.23±0.75	19.83±0.86
4	44.52±0.22	26.25±0.38	24.95±0.54
5	53.71±0.66	32.43±0.23	30.22±0.46
6	62.98±0.17	39.93±0.64	37.14±0.76
7	73.61±0.16	48.05±0.61	45.21±0.87
8	80.56±0.14	55.44±0.88	51.76±0.34
9	82.88±0.27	62.58±0.38	60.21±0.43
10	84.23±0.25	74.38±0.81	71.86±0.54
11	86.36±0.31	85.21±0.29	74.82±0.25
12	87.75±0.84	95.32±0.71	76.11±0.43

Table No 4: *In-vitro* release profile of Felodipine transdermal patches from F4 to F6

Time (hr)	F4	F5	F6
0	0	0	0
1	13.25±0.46	11.77±0.67	8.89±0.29
2	16.41±0.38	13.20±0.28	10.23±0.92
3	30.42±0.36	22.24±0.75	15.83±0.86
4	42.52±0.22	26.75±0.38	20.95±0.54
5	53.11±0.66	34.45±0.23	29.22±0.46
6	62.08±0.17	39.93±0.64	33.14±0.76
7	72.61±0.16	42.55±0.67	43.21±0.87
8	83.56±0.14	56.45±0.88	50.76±0.34
9	88.58±0.27	68.58±0.38	62.21±0.43
10	90.23±0.25	72.38±0.81	73.86±0.54
11	94.37±0.31	75.21±0.29	84.88±0.25
12	98.76±0.84	82.77±0.71	89.11±0.43

Table No 5: *In-vitro* release profile of Felodipine transdermal patches from F7 to F8

Time (hr)	F7	F8	F9
0	0	0	0
1	16.25±0.46	11.73±0.57	9.89±0.34
2	26.41±0.38	12.25±0.28	12.23±0.02
3	35.42±0.36	25.23±0.75	19.83±0.89
4	44.52±0.22	29.25±0.38	24.95±0.67
5	53.71±0.66	33.43±0.23	30.22±0.45
6	62.98±0.17	40.93±0.64	37.14±0.76
7	73.61±0.16	48.05±0.61	45.21±0.88
8	85.56±0.14	56.44±0.88	51.76±0.39
9	88.88±0.27	65.58±0.38	60.21±0.46
10	92.23±0.25	71.38±0.81	71.86±0.67
11	94.36±0.31	76.21±0.29	84.82±0.55
12	97.75±0.84	80.32±0.71	89.11±0.77

Table No.6 : *In-vitro* release profile of Felodipine transdermal patch through rat skin membrane: F1-F3

Time (hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	8.13±0.24	11.19±1.23	10.14±0.18	10.56±1.23	13.14±0.18	12.15±0.67
2	12.88±0.54	17.39±0.88	15.78±0.23	14.39±0.76	18.78±0.23	19.73±0.54
3	17.56±0.17	25.17±0.96	20.13±0.76	24.17±0.85	28.13±0.76	28.29±0.72
4	23.57±0.68	30.51±0.34	25.87±0.65	28.51±0.89	37.87±0.65	40.18±0.31
5	29.43±0.15	38.88±0.54	31.86±0.24	36.67±0.54	45.86±0.24	49.62±0.77
6	36.81±0.26	42.79±0.36	38.02±0.98	42.54±0.36	54.02±0.98	57.20±0.72
7	45.59±0.16	58.84±0.86	45.69±0.32	49.84±0.86	64.69±0.32	69.13±0.51
8	50.45±0.89	67.74±0.54	54.19±0.65	55.01±0.54	74.19±0.65	80.42±0.84
9	60.87±0.32	75.03±0.53	60.07±0.81	65.03±0.53	83.07±0.87	82.43±0.05
10	69.49±0.26	80.43±0.87	70.42±0.76	75.43±0.87	86.42±0.76	84.01±0.17
11	79.84±0.76	88.38±0.78	73.24±0.87	82.43±0.87	88.24±0.87	87.07±0.47
12	87.42±0.98	93.1±0.08	76.46±0.98	94.1±0.08	89.46±0.98	8N.12±0.29

Table No.7 : *In-vitro* release profile of Felodipine transdermal patch through rat skin membrane: F7-F9

Time (hr)	F7	F8	F9
0	0	0	0
1	12.14±0.18	11.15±0.67	12.10±0.67
2	17.78±0.23	18.73±0.54	17.73±0.04
3	20.45±0.76	28.29±0.43	27.29±0.40
4	25.07±0.65	39.18±0.31	36.18±0.32
5	33.86±0.24	45.62±0.19	44.62±0.19
6	39.02±0.98	55.20±0.72	58.20±0.72
7	45.69±0.32	66.13±0.51	67.13±0.57
8	58.19±0.65	80.42±0.84	72.42±0.84
9	65.07±0.81	81.43±0.05	79.43±0.56
10	78.42±0.76	83.01±0.17	80.91±0.15
11	83.24±0.87	86.07±0.47	83.33±0.47
12	92.46±0.12	88.00±0.29	84.77±0.29

Table No.8 : Stability study profile of selected Felodipine transdermal patch

Formulation code	Time in days	Appearance	%Drug content uniformity	%CDR
F2	0 day	Good	98.7±3.30	95.37±3.71
	30 days	Good	97.7±3.37	95.7±3.88
	60 days	Good	97.6±3.34	95.6±9.34
	90 days	Good	97.5±9.30	95.5±9.39
	180 days	Good	97.75±7.30	95.75±6.31
F4	0 day	Good	98.5±3.61	98.76±8.30
	30 days	Good	98.7±3.65	98.7±9.37
	60 days	Good	97.9±2.38	98.8±3.34
	90 days	Good	97.51±7.30	97.6±2.31
	180 days	Good	97.77±2.31	97.55±7.30
F5	0 day	Good	98.2±9.30	97.7±8.32
	30 days	Good	98.8±3.99	97.77±0.37
	60 days	Good	98.6±9.34	97.63±3.45

	90 days	Good	98.8±9.87	97.50±6.31
	180 days	Good	98.75±8.30	97.11±7.31

CONCLUSION:

Transdermal drug delivery represents one of the most rapidly advancing areas of novel drug delivery. Due to recent advances in technology and the ability to deliver the drug systemically without rupturing the skin membrane, transdermal route is becoming a widely accepted route of drug administration.

The transdermal system offers several advantages over oral dosage forms which include avoidance of hepatic first pass effect metabolism, decrease in frequency of administration, providing steady state plasma concentration and improves patient compliance etc.

Hence in this study an attempt was made to deliver Felodipine transdermal in order to provide a constant serum level of drug over the prolonged period of time. Polymers like HPMC,EC,Eudragit were selected for the study and were used at different concentrations. PEG 400 is incorporated as plasticizers in the formulations.

On evaluation of various parameter it was found that the polymers produced a satisfactory results with respect to the physical characteristics of the film and the release characteristics across synthetic membrane.FTIR for drug and drug with polymer were carried out and there is no interaction between drug and polymer.

A total of 9 formulations were made by using 3 different polymers.The formulated patches were subjected to physicochemical evaluator parameters like folding endurance, thickness, moisture uptake, moisture content, drug content to ascertain their integrity and physical stability. All the parameters were in IP limits.

Stability studies were carried out on the most satisfactory formulations like F2,F4 and F7 for two months as per ICH guidelines.There was no significant difference in the physicochemical parameters and *in vitro* drug release profiles. Hence the transdermal patch was successfully formulated by using Felodipine.

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