E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/13.02.11

Research Article

Formulation Optimization And Evaluation Of Evaluation Of Transdermal Drug Delivery System Of Felodipine

PRAVEEN ENDHARAPU*[1], SOMNATH DE[2], VENU MADHAV KATLA[3]
[1,2,3]St. pauls College of Pharmacy, Turkayamjal, Abdullapurmet , Ranga Reddy dist, Telangana, India-501510.
Received: 15.11.22, Revised: 02.12.22, Accepted: 07.01.23

ABSTRACT
Felodipine, a BCS class II calcium channel blocker, is utilized in the administration of hypertension and angina pectoris. Because of the unfortunate dissolvability and low bioavailability of the medication, there is a need to plan an elective course to accomplish a consistent plasma convergence of felodipine for its greatest remedial utility and can be accomplished by transdermal route.In this review, framework type transdermal patches were arranged utilizing various blends of hydrophilic polymer, to be specific, polyvinylpyrrolidone (PVP) and hydrophobic polymer, in particular, ethyl cellulose (EC) by dissolvable dissipation procedure and were oppressed for characterization.The Fourier change infrared examinations affirmed the similarity among medication and polymers. The patches F1 to F7exhibited uniform weight going from 153.3mg to 242.6mg And thickness of F1 to F7 are going from 0.133 to 0.22mm. Among the different clusters, the consistency weight and thickness shows that the polymeric arrangement of the medication is all around scattered in the patches. Every one of the details (F1 to F7) showed genuinely uniform medication content going from 95.77% to 98.67% individually. it is obviously demonstrated that the Felodipine transdermal patches containing Eudragit RS 100 in the proportion of 1:2 (F6) was the best detailing among the pre-arranged patches.

Keywords: Calcium channel blocker, Felodipine, Transdermal, Permeation.

INTRODUCTION
A recent approach of drug delivery is to deliver the drug into systemic circulation using skin as a site of application. Transdermal drug delivery (TDD) having potential to deliver the drug locally as well as systemically. It is gaining prominence over other forms of drug delivery because it offers a lot of advantages, including minimal trauma induction, avoid first pass metabolism, non-invasiveness, increased patient compliance, potential for continuous & controlled delivery.[1,2] The goal of transdermal patch designing is to maximize the flux into systemic circulation and simultaneously minimize the dose of the drug.[3]
Felodipine (dihydropyridine derivative) is a potent calcium channel blocker and used in the treatment of hypertension & angina pectoris. Felodipine effectively reduces blood pressure in hypertensive patients due to its vasodilatation effect on L-type calcium channels.[4,5] Its absorption is 100 % but undergoes CYP-3A4 dependent first pass metabolism in the intestine and liver. Thus the oral bioavailability is only 15% and more than 99% bound to plasma proteins. One of the major drawbacks in therapeutic application & efficacy of felodipine is its very low aqueous solubility. About 70% of total administered dose is excreted out as metabolites in urine. The usual dose of felodipine is 5-10mg daily with a maximum dose of 20mg daily. It causes rapid drop in systemic blood pressure and reflux tachycardia. So to avoid such adverse events, it should be given in extended dosage form.[5,6] Hence, transdermal drug delivery system is more suitable to avoid first pass metabolism, improve patient compliance, therapeutic efficacy, bioavailability and to reduce the frequency of dosing & its side effects.

MATERIALS AND METHODS

Materials

1	Felodipine	Srushti pharamaceuticals, Bengaluru
2	HPMC	S.D. Fine Chemicals Ltd., Mumbai, India.
3	Eudragit RS 100, Eudragit RL 100	Evoniks pharma Pvt. Ltd,Mumbai, India.
4	Dibutyl phalate	S.D. Fine Chemicals Ltd., Mumbai, India.
5	Oleic acid	Qualigens fine chemicals, Mumbai
6	Ethanol	Qualigens fine chemicals, Mumbai
7	Dichloromethane	Qualigens fine chemicals, Mumbai
8	Potassium dihydrogen Orthophosphate	S.d. fine chemical, Mumbai

METHODS

Preformulation studies

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

Description

Felodipine was physically examined for colour and odour etc.[70]

Solubility

The solubility of the selected drug was determined in distilled water and phosphate buffer of pH 7.4 using standard method.

Melting point

Fine powder of Felodipine was filled in glass capillary tube (previously sealed at one end) and kept in melting point apparatus. The melting point was found.[71, 72]

Compatibility Studies

Compatibility with Drug and Polymers was confirmed by carrying out IR studies

Estimation of Felodipine

A Spectrophotometric method based on the measurement of extinction at 236 nm in phosphate buffer of pH 7.4 was used for the estimation of Felodipine.

Preparation of phosphate buffer pH 7.4: [73]

0.2 M potassium dihydrogen phosphate was prepared and 250 ml of this solution was mixed with 195.5 ml of 0.2 M NaOH and volume was made upto 1000 ml with distilled water. The pH of the buffer was adjusted to 7.4

i) Standard graph of Felodipine Standard solution

An accurately weighed quantity of 100mg of Felodipine was dissolved in 100ml of buffer of pH 7.4. From this, 1ml was taken in a 100ml volumetric flask and the solution was made up to 100ml with phosphate buffer of pH 7.4.This solution was used as standard solution.

Procedure

The standard solution of Felodipine was subsequently diluted with phosphate buffer of pH 7.4 to obtain a series of dilutions containing 3, 6,9,12, and 15µg of Felodipine per 1ml of solution. The optical densities of the above dilutions were measured in UV spectrophotometer at 236 nm using the phosphate buffer of pH
7.4 as blank. The concentrations of Felodipine and corresponding optical densities are given in the Table 12. The optical densities were plotted against concentration of Felodipine and this calibration curve was used for estimating the Felodipine the samples.

Preparation of Transdermal patches

Table 2: Formulation of Felodipine patch

INGREDIENTS	Formulation Code						
	F1	F2	F3	F4	F5	F6	F7
Felodipine(mg)	20	20	20	20	20	20	20
HPMC(mg)	20	40	-	-	-	-	-
RL 100(mg)	-	-	20	40	-	-	20
RS 100(mg)	-	-	-	-	20	40	20
Oleic acid(ml)	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Dichloro methane(ml)	10	10	20	20	20	20	20
Ethanol(ml)	10	10	-	-	-	-	-
Dibutylphalate(%)	15%	15%	15%	15%	15%	15%	15%

The trasdermal patches were prepared by solvent evaporation method. Different polymers (Eudragit RS 100, Eudragit RL 100 and HPMC) alone and in combination were accurately weighed and dissololved in 20 ml solvent. Known volume of Dibutyl phalate was used as plasticizer and oleic acid used as permeation enhancer and mixed thoroughly with help of magnetic stirrer. 20 mg of drug was dissolved in the solution and mixed for 10mins. The resulted uniform solution was poured into petridish and kept for the evapouration after 24hrs a dried film were out and stored in desiccators.

Evaluation of Transdermal patches

The prepared Felodipine transdermal patches were evaluated as mentioned below.

1. Weight variation
2. Thickness uniformity
3. Moisture content
4. Moisture uptake
5. Tensile Strength
6. Folding Endurance
7. Drug content
8. Water vapour transmission (WVT) rate
9. *In vitro* drug release studies
10. Stability Studies

Uniformity of weight

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

Thickness of the patch

The thickness of the patch was assessed by using digital vernier caliper 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.

Moisture content

The patches were weighed individually and kept in a dessicator containing calcium chloride at 37^{o}C for 24 hrs. The final weight was noted when there was no change in the weight of individual patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

Moisture uptake

A weighed film kept in desiccator at 40^{o}C for 24h was taken out and exposed to relative humidity of 93%RH (saturated solution of Potassium bromide) in a desiccator at room temperature then the weights were measured periodically to constant weights.

Determination of tensile strength

The tensile strength is determined as stretching force applied to the sample at which point it breaks. These measurements were performed on a dumbbell shaped specimen. A specified weight was hung from the film through the specimen such that a pulling force was created. The force applied on the load cell of the apparatus was measured in kg/cm^{2}.

Folding Endurance

This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

Drug content determination

The patches at 1Cm^2 were cut and added to a beaker containing 100ml of Phosphate buffered solution of pH 7.4. The medium was stirred with a magnetic bead for 5hrs. The solution was later filtered and analyzed for drug content with proper dilution at 236 nm spectrophotometrically.

Water vapour transmission (WVT) rate:

The film was fixed over the brim of a glass vial, containing 3 g of fused calcium chloride as desiccant, with an adhesive tape. The vial was weighed and kept in desiccator containing saturated solution of potassium chloride to provide relative humidity of 84%. The vial was taken out and weighed at every 24 hrs intervals for a period of 72 hrs. The WVT was calculated by taking the difference in the weight of the patches before and at regular intervals of 24 hrs.

In-vitro drug release studies:

In-vitro Drug Release

The fabricated film was placed on the semi permeable membrane and attached to the modified diffusion cell such that the cell's drug releasing surface towards the receptor compartment which was filled with phosphate buffer solution of pH 7.4 at 37$\pm1^0$C. The elution medium was stirred magnetically. The aliquots (5ml) were withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 7.4. The samples were analyzed for drug content using UV spectrophotometer at 236 nm.

Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q0-Q) v/s t], Higuchi's square root of time (Q v/s √t) and Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q0-Q) is the cumulative percentage of drug remaining after time t.

Stability studies

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. One formulation was selected for stability studies on the basis of physiochemical characteristics, *in vitro* drug release of the formulations. The formulation was subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines. The most satisfactory formulation was sealed in an aluminum foil and stored at 30 ± 2 ºC, 65 ± 5% RH and at 40 ± 2 ºC, 75 ± 5% RH for 2 month. Patches were periodically removed and evaluated.

RESULTS

Preformulation Studies

Description

Felodipine was physically examined for colour. It is white amorphous powder.

Solubility

Felodipine was freely soluble in water, methanol, acetone and other organic solvents.

Melting point

The melting point of Felodipine was found to be 210^0C.

Compatibility Studies

The results of compatibility studies are shown in Fig 14 to 21.

Preparation of standard calibration curve of Felodipine

The standard calibration curve of Felodipine was shown in Table 12 and Fig 22.

Evaluation of Transdermal patches

Weight of the patch

The Weight of Transdermal patches of F1 to F7 varies from 153.3mg to 242.6mg and is given in the Table 7.

Thickness of the patch

Thickness of Transdermal patches varies from 0.133 to 0.22mm of F1 to F7 is shown in Table 8.

Moisture content

Moisture content of Transdermal patches from F1 to F7 is shown in Table 9.

Moisture uptake

Moisture uptake of Transdermal patches from F1 to F7 is shown in Table 9.

Tensile Strength

Tensile Strength of Transdermal patches varies from 1.697 to 2.866 of F1 to F7 is shown in the Table 10.

Folding Endurance

Folding Endurance of Transdermal patches varied from 201 to 243.6 of F1 to F7 and is

shown in Table10.

Drug content determination

Drug content of Transdermal patches, F1 to F7 varies between 95.77% to 98.67% and is shown in Table 11.

Water Vapour Transmission Rate

Water Vapour Transmission rate of Transdermal patches from F1 to F7 varies in the range 1.59 to 4.21 and is shown in the Table 11.

In vitro drug release studies

The maximum cumulative % drug release for formulation F1 to F7 are shown in the Table 13 to 19.

In vitro release profiles are shown (Fig 23). The data obtained was fitted to zero order, first order, and Higuchi's square root of time and Korsemeyer-Peppas equations to understand the mechanism of drug release from the Felodipine Transdermal patches (Fig 26). The slopes and the regression co-efficient determinations (R^2) are listed in Table 20. The co-efficient determination indicated that the release data was best fitted with zero order kinetics. Higuchi equation explains the diffusion controlled release mechanism.

Stability Studies

Physiochemical evaluation of F6 during Stability Studies and Drug diffusion profile of F6 during Stability Studies are shown in the Table 21 and 22, Diffusion profile for optimized formulation F6 are shown in Fig 27.

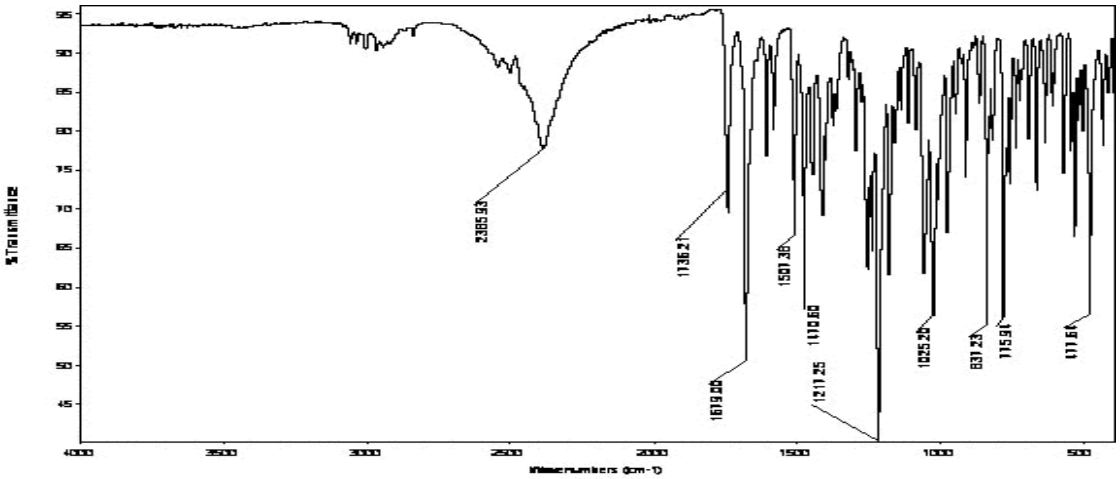

Fig 1: IR Spectrum of Felodipine

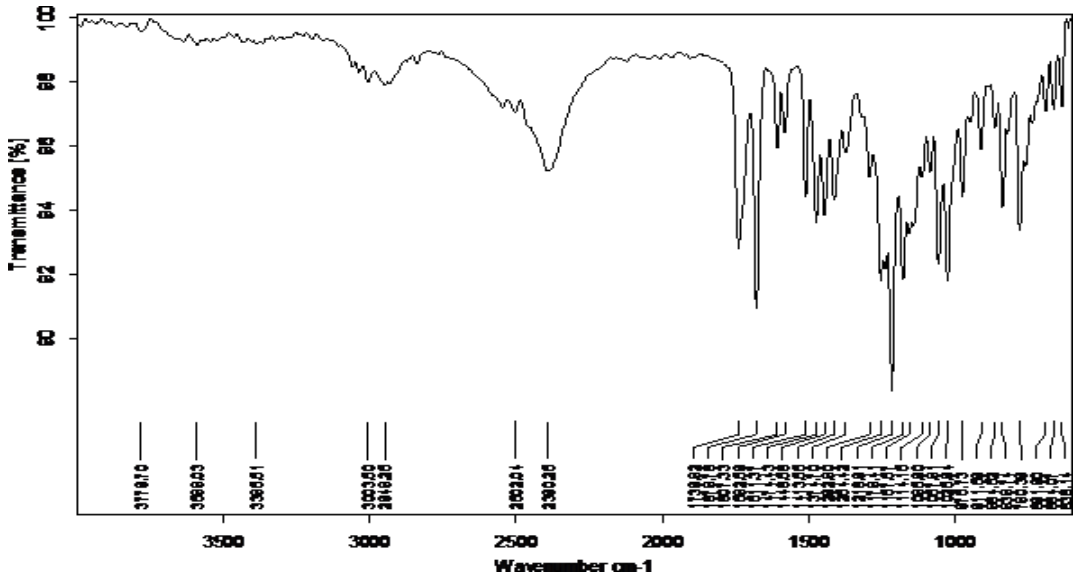

Fig 2: IR Spectrum of Felodipine , Eudragit RS 100 and Eudragit RL 100

Table 2: Weight Variation

Sl no	Formulation	Tria1(mg)	Tria2(mg)	Tria3(mg)	Avg(mg)
1	F1	151	156	153	153.3±2.5
2	F2	240	244	244	242.6±2.3
3	F3	167	164	168	166.3±2.0
4	F4	238	239	238	238.5±0.5
5	F5	170	169	175	171.3±3.2
6	F6	222	228	229	226.3±3.7
7	F7	180	183	181	181.4±1.5

Table 3: Thickness Uniformity

Sl no	Formulation	Tria1(mm)	Tria2(mm)	Tria3(mm)	Avg(mm)
1	F1	0.16	0.16	0.16	0.16±0.01
2	F2	0.19	0.18	0.19	0.185±0.005
3	F3	0.13	0.13	0.14	0.133±0.005
4	F4	0.19	0.2	0.21	0.2±0.1
5	F5	0.16	0.17	0.17	0.166±0.005
6	F6	0.21	0.22	0.23	0.22±0.01
7	F7	0.21	0.2	0.21	0.206±0.005

Table 4: Moisture content and Moisture Uptake

Sl no	Formulation	%Moisture content	%Moisture uptake
1	F1	4.8±0.02	7.69±0.01
2	F2	5.15±0.02	10.59±0.01
3	F3	4.39±0.01	5.34±0.03
4	F4	4.69±0.02	6.18±0.01
5	F5	2.38±0.02	4.41±0.02
6	F6	2.78±0.02	4.59±0.02
7	F7	3.47±0.02	4.87±0.02

Table 5: Tensile strength and Folding endurance

Sl no	Formulation	Tensile strength (Kg) (n=3)	Folding endurance(n=3)
1	F1	1.697±0.005	201±8.71
2	F2	2.841±0.009	241±10.58
3	F3	2.934±0.006	207.3±7.5
4	F4	1.845±0.003	224±25.57
5	F5	1.697±0.005	201.6±3.05
6	F6	2.866±0.005	243.6±5.13
7	F7	2.762±0.03	232.5±6.35

Table 6: Drug content and Water vapour transmission rate

Sl no	Formulation	Drug content (%)	Water vapour transmission rate (gm/ cm^2/hr)× 10^{-4}
1	F1	97.68±0.01	3.99
2	F2	96.59±0.01	4.21
3	F3	96.86±0.01	1.784
4	F4	95.77±0.01	1.59
5	F5	97.15±0.01	3.22
6	F6	98.67±0.01	3.7
7	F7	98.11±0.01	2.5

Table 7: Data for Calibration Curve of Felodipine in phosphate buffer pH 7.4 at 236nm

Sl no	Concentration (µg/ml)	Absorbance
1	0	0
2	3	0.162
3	6	0.321
4	9	0.478
5	12	0.621
6	15	0.78

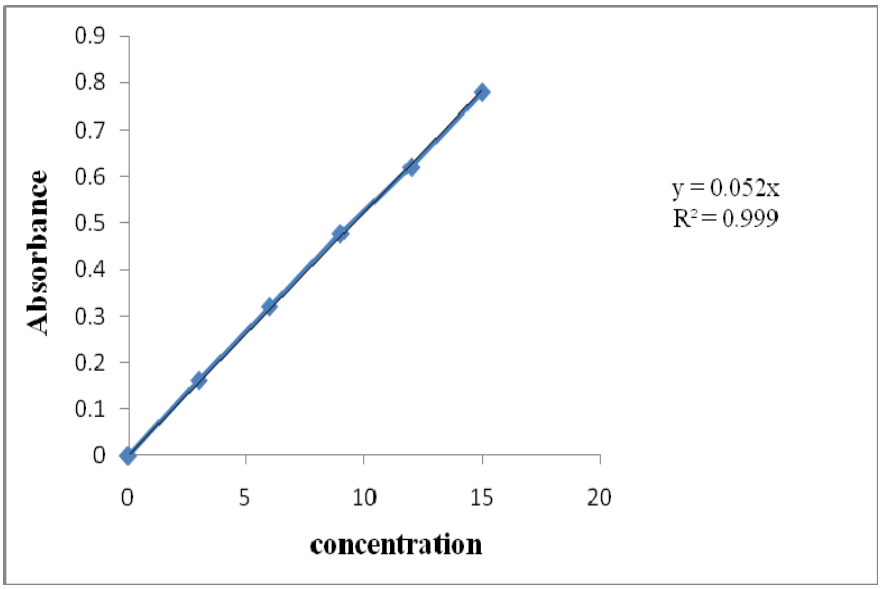

Fig 3: Standard calibration curve of Felodipine in phosphate buffer pH 7.4 at 236nm

Table 8: *In-vitro* drug release profile of Felodipine transdermal patch (F1)

Sl.no	*Time (hrS)*	*√T*	*Log T*	*Cumulative % of drug released*	*Log Cumulative % drug released*	*Cumulative % of drug remained*	*Log Cumulative % drug remained*
1	1	1	0	4.079136	0.610568	95.92086	1.981913
2	2	1.414	0.301	7.321449	0.864597	92.67855	1.966979
3	3	1.732	0.477	15.37777	1.186893	84.62223	1.927484
4	4	2	0.602	23.91633	1.378695	76.08367	1.881291
5	5	2.236	0.698	32.15137	1.507199	67.84863	1.831541
6	6	2.449	0.778	37.48908	1.573905	62.51092	1.795956
7	7	2.645	0.845	43.36178	1.637107	56.63822	1.75311
8	8	2.828	0.903	50.12015	1.700012	49.87985	1.697925
9	9	3	0.954	55.78465	1.746515	44.21535	1.645573
10	10	3.162	1	61.43112	1.788388	38.56888	1.586237
11	11	3.316	1.041	66.53504	1.82305	33.46496	1.52459
12	12	3.464	1.079	71.18272	1.852375	28.81723	1.459653

Table 9: *In-vitro* drug release profile of Felodipine transdermal patch (F2)

Sl.no	Time (hrs)	√T	Log T	Cumulative % of drug released	Log Cumulative % drug released	Cumulative % of drug remained	Log Cumulative % drug remained
1	1	1	0	3.642085	0.56135	96.35791	1.983887
2	2	1.414	0.301	7.903311	0.897809	92.09669	1.964244
3	3	1.732	0.477	13.74641	1.138189	86.25359	1.935777
4	4	2	0.602	21.99034	1.342232	78.00966	1.892148
5	5	2.236	0.698	28.00716	1.447269	71.99284	1.857289
6	6	2.449	0.778	36.89129	1.566924	63.10871	1.800089
7	7	2.645	0.845	42.24879	1.625814	57.75121	1.761561
8	8	2.828	0.903	48.1453	1.682554	51.8547	1.714788
9	9	3	0.954	54.38617	1.735488	45.61383	1.659097
10	10	3.162	1	60.18889	1.779516	39.81111	1.600004
11	11	3.316	1.041	64.74811	1.811227	35.25189	1.547182
12	12	3.464	1.079	67.52749	1.829481	32.47251	1.511516

Table 10: In-vitro drug release profile of Felodipine transdermal patch (F3)

Sl.no	Time (hrs)	√T	Log T	Cumulative % of drug released	Log Cumulative % drug released	Cumulative % of drug remained	Log Cumulative % drug remained
1	1	1	0	4.2633	0.629746	95.7367	1.981078
2	2	1.414	0.301	8.348958	0.921632	91.65104	1.962137
3	3	1.732	0.477	16.1816	1.209021	83.8184	1.923339
4	4	2	0.602	23.10482	1.363703	76.89518	1.885899
5	5	2.236	0.698	28.2032	1.450298	71.7968	1.856105
6	6	2.449	0.778	33.10189	1.519853	66.89811	1.825414
7	7	2.645	0.845	37.81488	1.577663	62.18512	1.793686
8	8	2.828	0.903	42.87233	1.632177	57.12767	1.756847
9	9	3	0.954	48.11455	1.682276	51.88545	1.715046
10	10	3.162	1	54.12462	1.733395	45.87538	1.66158
11	11	3.316	1.041	57.40764	1.75897	42.59236	1.629332
12	12	3.464	1.079	60.20168	1.779609	39.79832	1.599865

Table 11: In-vitro drug release profile of Felodipine transdermal patch (F4)

Sl.no	Time (hrs)	√T	Log T	Cumulative % of drug released	Log Cumulative % drug released	Cumulative % of drug remained	Log Cumulative % drug remained
1	1	1	0	4.224819	0.625808	95.77518	1.981253
2	2	1.414	0.301	7.613107	0.881562	92.38689	1.96561
3	3	1.732	0.477	14.94159	1.174397	85.05841	1.929717
4	4	2	0.602	21.11921	1.324678	78.88079	1.896971
5	5	2.236	0.698	26.28931	1.419779	73.71069	1.86753
6	6	2.449	0.778	31.99411	1.50507	68.00589	1.832547
7	7	2.645	0.845	36.95264	1.567645	63.04736	1.799667
8	8	2.828	0.903	40.23101	1.604561	59.76899	1.776476

9	9	3	0.954	46.69168	1.669239	53.30832	1.726795
10	10	3.162	1	51.47516	1.711598	48.52484	1.685964
11	11	3.316	1.041	54.22843	1.734227	45.77157	1.660596
12	12	3.464	1.079	58.76433	1.769114	41.23567	1.615273

Table 12: *In-vitro* drug release profile of Felodipine transdermal patch (F5)

Sl.no	Time (hrs)	√T	Log T	Cumulative % of drug released	Log Cumulative % drug released	Cumulative % of drug remained	Log Cumulative % drug remained
1	1	1	0	5.506833	0.740902	94.49317	1.9754
2	2	1.414	0.301	8.606313	0.934817	91.39369	1.960916
3	3	1.732	0.477	15.43102	1.188395	84.56898	1.927211
4	4	2	0.602	20.45058	1.310706	79.54942	1.900637
5	5	2.236	0.698	25.12402	1.400089	74.87598	1.874343
6	6	2.449	0.778	29.28225	1.466604	70.71775	1.849528
7	7	2.645	0.845	34.87638	1.542531	65.12362	1.813739
8	8	2.828	0.903	38.17976	1.581833	61.82024	1.791131
9	9	3	0.954	44.14103	1.644842	55.85897	1.747093
10	10	3.162	1	49.96836	1.698695	50.03164	1.699245
11	11	3.316	1.041	53.56363	1.72887	46.43637	1.666858
12	12	3.464	1.079	56.00041	1.748191	43.99959	1.643449

Table 13: *In-vitro* drug release profile of Felodipine transdermal patch (F6)

Sl.no	Time (hrs)	√T	Log T	Cumulative % of drug released	Log Cumulative % drug released	Cumulative % of drug remained	Log Cumulative % drug remained
1	1	1	0	2.913668	0.46444	97.08633	1.987158
2	2	1.414	0.301	7.901857	0.897729	92.09814	1.964251
3	3	1.732	0.477	14.44423	1.159695	85.55577	1.932249
4	4	2	0.602	20.24209	1.306255	79.75791	1.901774
5	5	2.236	0.698	24.12843	1.382529	75.87157	1.880079
6	6	2.449	0.778	27.2649	1.435604	72.7351	1.861744
7	7	2.645	0.845	32.53451	1.512344	67.46549	1.829082
8	8	2.828	0.903	36.6782	1.564408	63.3218	1.801553
9	9	3	0.954	41.1214	1.614068	58.8786	1.769957
10	10	3.162	1	45.34023	1.656484	54.65977	1.737668
11	11	3.316	1.041	49.27595	1.692635	50.72405	1.705214
12	12	3.464	1.079	52.46179	1.719843	47.53821	1.677043

Table 14: In-vitro drug release profile of Felodipine transdermal patch (F7)

Sl.no	Time (hrs)	√T	Log T	Cumulative % of drug released	Log Cumulative % drug released	Cumulative % of drug remained	Log Cumulative % drug remained
1	1	1	0	3.787769	0.578383	96.21223	1.98323
2	2	1.414	0.301	7.670508	0.884824	92.32949	1.96534
3	3	1.732	0.477	13.57141	1.132625	86.42859	1.936657
4	4	2	0.602	18.40601	1.26496	81.59399	1.911658

5	5	2.236	0.698	25.20236	1.401441	74.79764	1.873888
6	6	2.449	0.778	31.89565	1.503732	68.10435	1.833175
7	7	2.645	0.845	37.49501	1.573974	62.50499	1.795915
8	8	2.828	0.903	42.08564	1.624134	57.91436	1.762786
9	9	3	0.954	46.97665	1.671882	53.02335	1.724467
10	10	3.162	1	51.41107	1.711057	48.58893	1.686537
11	11	3.316	1.041	55.184	1.741813	44.816	1.651433
12	12	3.464	1.079	58.84772	1.76973	41.15228	1.614394

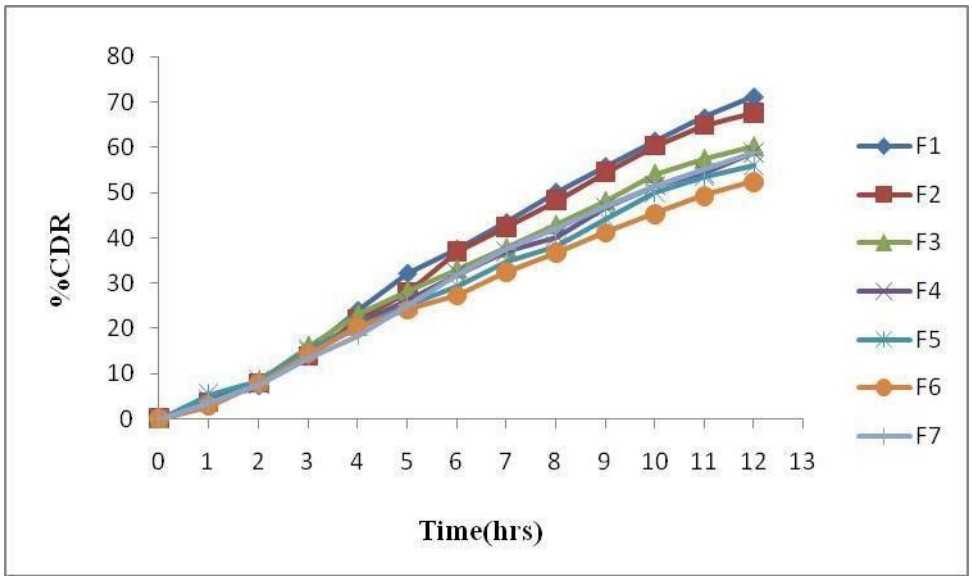

Fig 4: *In-vitro* release profile of Felodipine Tansdermal patches (F1 to F7) %CDR *vs* TIME

Table 15: Regression co-efficient (R^2) values of Felodipine transdermal patches according to different kinetic models

Formulation	Zero order	First order	Higuchi	Peppas	'n' values for Peppas
F1	0.994	0.988	0.916	0.987	0.602
F2	0.993	0.990	0.910	0.993	0.571
F3	0.994	0.995	0.932	0.990	0.653
F4	0.995	0.996	0.927	0.991	0.627
F5	0.997	0.991	0.928	0.994	0.709
F6	0.995	0.997	0.933	0.984	0.554
F7	0.994	0.992	0.917	0.995	0.58

Stability studies

Table 16: Physicochemical evaluation of formulation F6 during stability studies

Parameters	0 days*	30 days*		60 days*	
		A	B	C	D
Weight Uniformity (mg)	226.3±3.78	226±0.23	223.35±3.5	226±0.9	222.43±3.12
Folding endurance	243.6±5.13	240±5.34	238±4.76	237±4.78	235±3.65
Patch thickness (mm)	0.22±0.01	0.22±0.03	0.21±0.03	0.21±0.002	0.21±0.004

% Drug content	98.67	98.55	98.4	98.37	98.35
%Moisture Content	2.78	2.7	2.68	2.6	2.55
%Moisture uptake	4.59	4.53	4.48	4.52	4.49
WVTR ($gm/cm^2/hr$)× 10^{-4}	3.7	3.63	3.59	3.58	3.56
Tensile strength(Kg)	2.866±0.00	2.859±0.005	2.855±0.004	2.847±0.007	3.832±0.003

* All values are the mean of three readings ± SD A, C: 30 ± 2°C/ 65 ± 5% RH
B, D: 40 ± 2°C/ 75 ± 5% RH

Table 17: Drug diffusion profile of formulation F6 during stability studies

Time (Hrs)	After 30 days*		After 60 days*	
	A	B	C	D
1	3.01	2.99	2.95	2.98
2	7.83	7.65	7.5	7.81
3	14.99	15.61	15.71	15.01
4	21.12	22.28	22.35	23.23
5	24.1	25.34	24.91	25.09
6	27.17	27.98	27.09	27.91
7	31.72	32.05	31.82	31.54
8	36.52	36.41	35.88	35.55
9	40.02	40.73	39.73	39.03
10	44.71	43.85	43.09	42.75
11	48.24	47.39	46.55	46.41
12	51.95	51.18	51.05	50.93

* All values are the mean of three readings ± SD A, C: 30 ± 2°C/ 65 ± 5% RH
B, D: 40 ± 2°C/ 75 ± 5% RH

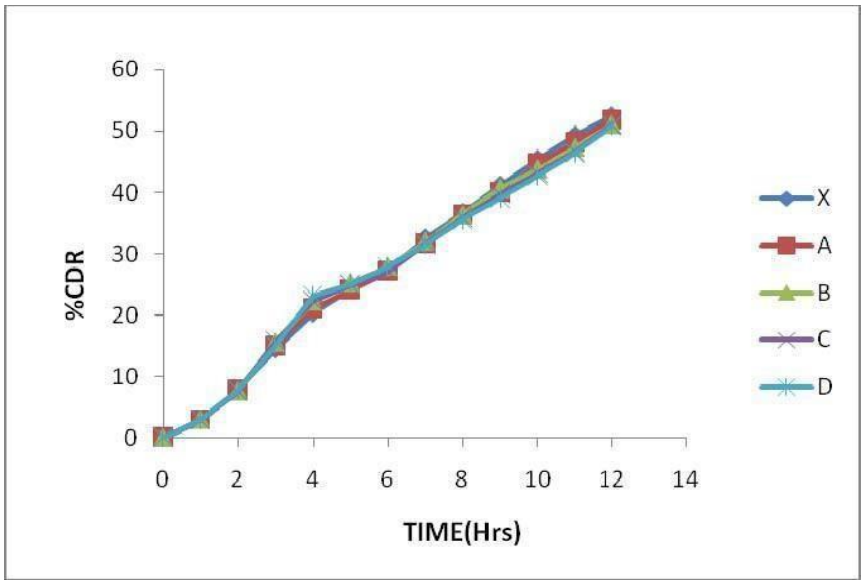

Fig 5: Comparision of *In-vitro* diffusion profile of F6 formulation during stability studies and before stability studies

DISCUSSION

Method was developed for the estimation of Felodipine and showed maximum absorption at wavelength 236 nm in phosphate buffer pH 7.4. The standard calibration curve obeyed Beer's law at the given concentration range of 3µg/ml to 15µg/ml.

In order to investigate the possible interaction between drug and selected polymers, FT-IR spectroscopy studies were carried out. IR spectrum for pure drug and physical mixture of drug-polymers were obtained and characterised.

It was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. The results are given in the figure 14 to 21.

Transdermal patches of Felodipine were prepared by using polymers, like HPMC, Eudragit RL100 and Eudragit RS100. The patches were transparent, smooth and flexible. The results of weight variation, thickness, moisture content, moisture uptake, Folding Endurance, Tensile strength, drug content are shown in table 7 to table 11.

The patches F1 to F7exhibited uniform weight ranging from 153.3mg to 242.6mg And thickness of F1 to F7 are ranging from 0.133 to 0.22mm.

Among the various batches, the uniformity weight and thickness indicates that the polymeric solution of the drug is well dispersed in the patches. All the formulations (F1 to F7) exhibited fairly uniform drug content ranging from 95.77% to 98.67% respectively.

The moisture uptake and Moisture content was found to be low in formulation F3, F4, F5, F6 and F7. This is because of hydrophobic nature of Eudragit polymer compared to HPMC.

Folding Endurance of the developed formulations F1 to F7 varied from 201 to 243.6. The highest folding endurance was noted for formulation F6. Data was recorded in Table 10.

The tensile strength test provides an indication of the strength and elasticity of the film which is reflected by the tensile strength and elongation of the break. Transdermal patches should preferably be strong and flexible. The Transdermal patch preparations differed in tensile strength. Tensile Strength of F1 to F7 varied from 1.697 Kg to 2.866 Kg. The results were shown in table 10.

The *in vitro* permeation studies of patches using cellophane membrane barrier was carried out using modified diffusion cell. The results of *in vitro* permeation studies are shown in the Table 13 to Table 19.

The cumulative percentage of drug permeated from F1 to F7 formulations was given in the following order F1 > F2 > F3 > F7> F4 > F5> F6.

From the graph it is evident that drug release is decreased with the increase in concentration of polymer. Eudragit RS 100 and Eudragit RL100 patches have also shown decreased drug release when compared to HPMC patches.

The release kinetics was evaluated by making use of Zero order, First order, Higuchi's diffusion and Korsemeyer – Peppa's equation. The drug release through the transdermal patches of Felodipine follows First order kinetics with diffusion controlled mechanism.

By fitting in the Korsemeyer –Peppa's equation the release kinetics follows non-Fickian kinetics. The range of 'n' value for Korsemeyer - Peppa's equation -1 to

If the 'n' values of Korsemeyer – Peppa's equation is below 0.5, which indicates Fickian kinetics. If the 'n' value of Korsemeyer – Peppa's equation is in between 0.5 to 1, this indicates non-Fickian kinetics. Here the patches of Felodipine release kinetics fitted in Korsemeyer – Peppa's equation. 'n' values are in between 0.5 to 1, so the release is following non- Fickian, diffusion controlled kinetics.

The stability studies were carried out on the most satisfactory formulations F6 at 30 ± 2°C/ 65 ± 5% RH and 40 ± 2°C/ 75 ± 5% RH for two months to assess their long term stability as per ICH guidelines. At fixed time intervals of 30 days and 60 days, the formulation was evaluated for the physicochemical properties, *in vitro* drug release. There was no significant difference in the physicochemical parameters, *in vitro* drug release profiles were found to be super impossible with the initial readings at zero day results. The results are shown in table 21, 22 and figure 27.

CONCLUSION

The preformulation studies involving description, solubility, melting point, of the drug were found to be comparable with the standard. Based on the all the above preformulation studies the drug was suitable for making the transdermal formulation.

Based on all these factors the transdermal drug delivery system F1 is having greater % drug release. Formulation F6 having less drug release capacity than other formulations. The formulation F6 shows better extended release up to 12 hrs when compared to other formulations.

So it was concluded that the formulation F6 prepared by using Eudragit RS 100(1:2 ratio)is the better formulation for control release of drug up to 12 hrs of time. However the *in vitro* drug

release of the best formulation F6 follows first order kinetics and the mechanism of diffusion. Results of the present study encouraged that the Felodipine with Eudragit RS 100 transdermal patch can be used as controlled drug delivery system and frequency of administration can be minimized.

The stability studies were carried out on the most satisfactory formulations F6 at 30 ± 2°C/ 65 ± 5% RH and 40 ± 2°C/ 75 ± 5% RH for two months to assess their long term stability as per ICH guidelines. At fixed time intervals of 30 days and 60 days, the formulation was evaluated for the physicochemical properties, *in vitro* drug release. There was no significant difference in the physicochemical parameters, *in vitro* drug release profiles were found to be super impossible with the initial readings at zero day results. The results are shown in tables 21, 22 and figure 27.

From the above studies, it is clearly indicated that the Felodipine transdermal patches containing Eudragit RS 100 in the ratio of 1:2 (F6) was the best formulation amongthepreparedpatches.

ACKNOWLEDGEMENT

The Authors are thankful to St pauls college of pharmacy, Hyderabad for providing the necessary facilities for the research work.

REFERENCES

1. KandavalliS,Nair V Panchagnula R. Polymers in transdermal drug delivery systems pharmaceutical Technology 2002, 62-78. Available from: http://www.pharmtech.com/.
2. GuyRH. Current status and future prospects of transdermal drug delivery, Pharm Res 1996, 13, 1765-1769.
3. Guy RH, Hadgraft J, Bucks DA. Transdermal drug delivery and cutaneous metabolism, Xenobiotica 1987, 7, 325-343.
4. Chein YW. Transdermal Controlled Systemic Medication. New York andBasel, Marcel Dekker Inc. 1987; 159 – 176.
5. Comfort AR, Sherchuk I, Ohe JH, Dinh SM. In-vitro characterization of a solvent controlled nitroglycerine transdermal system. J Controlled Rel 1995; 34-.193-201.Carpel MC, Erasmo AME, Rawena SW, Elizebath PH, Rondoll Z. Drug Intelligence Clinical Pharmacy; 1987.
6. Chien Yie W. Transdermal drug delivery and delivery systems. 2nd Ed. New York: Marcel Dekkar Inc; 1992.
7. Obsorne, Hattzenbuler. The influence of skin surface lipids on topical formulations. New York: Marcel Dekker Inc; 1990.
8. Marjukka ST, Bouwsira JA, Urtti A. Chemical enhancement of percutaneous absorption in relation to stratum corneum structural alterations. J Control Rel 1999; 59:149-61.
9. Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov 2004; 3(2):115-24.
10. Chatterjee CC. Human physiology. Medical allied agency. Vol II. Calcutta India: p1:p680.
11. Guy RH. Current status and future prospects of transdermal drug delivery.Pharm Res 1996;13(12):1765-69.
12. Hadgraft J. Recent developments in topical and transdermal delivery. Eur J Drug Metab Pharmacokinetic 1996; 21:165-73.
13. Hadgraft J. Passive enhancement strategies in topical and transdermal drug delivery. Int J Pharm 1999; 184:1-6.
14. Kydoneius AF. Fundamentals of transdermal drug delivery, CRC Press, Boca Raton Florida; 1987:3.
15. Franz TJ, Tojo K, Shah KR, Kydonieus AF. Treatise on controlled drug delivery, Marcel Dekker, New York; 341-421.
16. Vecchia BE, Bunge AL. Transdermal drug delivery, 2nd edition, Marcel Dekker, New York; 25-55. Pongjanyakul T, Prakongpan S, Priprem A. Acrylic matrix type nicotine transdermal patches: In-vitro evaluation and batch-to-batch uniformity. Drug Dev Ind Pharm 2003; 29(8):843-53.
17. Shin SC, Shin EY, Cho CW. Enhancing effects of fatty acid on piroxicam permeation through rat skins. Drug Dev Ind Pharm 2000; 26(5):563-6.
18. Tipre DN, Vavia PR. Formulation, optimization and stability study of transdermal therapeutic system of nicorandil. Pharm Dev Technol 2002; 7(3):325-32.
19. Verma PRP, Iyer SS. Controlled transdermal delivery of propranolol using HPMC matrices: Design and *in-vitro* and *in-vivo* evaluation. J Pharm Pharmacol 2000; 52:151-6.
20. Jamakandi VG, Mull JS, Vinay BL, Shivakumar HN. Formulation, characterization, and evaluation of matrix-type transdermal patches of a model anti-hypertensive drug. Asian J Pharm 2009; 59-65.
21. Nguyen Thien Hai, Juyoun Kim, Eun-Seok Park, Sang-Cheol Chi.
22. Formulation and biopharmaceutical evaluation of transdermal patch containing benztropine
23. Int J Pharm 2008; 357:55-60.
24. Christopher Jeans W, Charles Heard M. A therapeutic dose of primaquine can be delivered across excised human skin from simple transdermal patches. Int J Pharm 1999; 189:1-6.
25. Soodabeh Davaran, Mohammad Rashidi R, Reza Khandaghi, Mahdi Hashemi.
26. Development of novel prolonged-release nicotine transdermal patch. Pharmacol Res 2005; 51:233-237.
27. Manvi FV, Dandagi PM. Formulation of transdermal drug delivery system of ketotifen

fumarate. Ind J Pharm ***sci***. 2003; 65(3):239-243.
28. Shankar V, Benito D. Design and evaluation of Nifedipine transdermal patches. Ind J pharm Sci. 2003; 65(5):510-515.
29. Gurol Z. *Invitro* release and percutaneous absorption of ketoprofen from defferent ointment bases. Pharma Acta Helv 1996; 71(3): 205-12. . Gurol Z. *Invitro* release and percutaneous absorption of ketoprofen from defferent ointment bases. Pharma Acta Helv 1996; 71(3): 205-12.
30. Durran NJ, Singh SK. Effect of permeation enhancers on release of ketoprofen through TDDS. Pharmazie 1996; 51(10): 741-44.
31. Almirall M. Effect of d-limonene on permeation profile of haloperidol. 1996; 46(7): 676-80.
32. Kunta JR, Goskonda VR, Botherton HO, Khan MA, Reddy IK. Effect of menthol and related terpenes on percutaneous absorption of propranalol across excised hairless mouse skin. J Pharma Sci.1997; 86(12): 1369-73.
33. Narasimha murthy S, Mini sateesh, Hamsa V. Drug release from terbutaline sulphate transdermal films across human cadaver skin. Indian. J Pharma Sci1997; 59(2): 75-76.
34. Rama Rao P, Diwan P. Formulation and evaluation of polymeric films of indomethacin for transdermal administration. Ind J Pharma Sci 1998; 169-171.
35. Doddayya Hiremath, Prasanna sagar. Comparison studies of skin permeability of verapamil transdermal films across mice and human cadaver skins. Indian drugs 2001; 38(12): 649.