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FORMULATION AND CHARACTERISATION OF TRANSDERMAL PATCHES OF PERINDOPRIL

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ABSTRACT

Transdermal drug delivery system (TDDS) has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery of drugs. The skin as a site of drug delivery, has a number of significant advantages over many other routes of drug administration, including the ability to avoid problems of gastric irritation, pH and emptying rate effects, avoid hepatic first-pass metabolism thereby increasing the bioavailability of drug, reduce the risk of systemic side effects by minimizing plasma concentrations compared to oral therapy, provide a sustained release of drug at the site of application; rapid termination of therapy by removal of the device or formulation, the reduction of fluctuations in plasma levels of drugs, and avoid pain associated with injections. The transdermal delivery can also eliminate pulsed entry into the systemic circulation, which might often cause undesirable side effects. Main objective of formulating the transdermal system was to prolong the drug release time, reduce the frequency of administration and to improve patient compliance. In the present study, five formulations were prepared using single polymer in different ratios, along with plasticizers and penetration enhancer. Finally it was concluded that Some formulations show formation of brittle patch due to insufficient amount of polymer and in some patches texture of patch is not elegant due to plasticizer concentration for patch preparation. So by increasing concentration of polymer and plasticizer, finally formulation-5 was considered as optimized formula for preparing transdermal patch of Perindopril, where it shown best drug release profile.

Keywords: Perindopril, Transdermal Patch, Transdermal drug delivery system

INTRODUCTION

Transdermal drug delivery

An Introduction [1, 2]

Until recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven effective delivery through the skin-typically cardiac drugs such as nitroglycerin and hormones such as estrogen. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. The basic components of any transdermal delivery system include the drug(s) dissolved or dispersed in a reservoir or inert polymer matrix; an outer backing film of paper, plastic, or foil; and a pressure-sensitive adhesive that anchors the patch to the skin. The adhesive is covered by a release liner, which needs to be peeled off before applying the patch to the skin. Drugs administered via skin patches include scopolamine, nicotine, estrogen, nitroglycerin, and lidocaine. Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories therapeutic and cosmetic), aroma patches, weight loss patches, and patches that measure sunlight exposure.

MATERIALS AND EQUIPMENTS

Table 1: List of Materials used:

S.NO	MATERIALS	SUPPLIER
1	PERINDOPRIL	SIGMA-ALDRICH INDIA, MUMBAI
2	HPMC(mg)	COLORCON INDIA, MUMBAI
3	EUDRAGIT-L 100	EVONIK INDUSTRIES
4	CARBOPOL-971P	S.D.FINE CHEMICALS
5	PROPYLENE GLYCOL(mg)	S.D.FINE CHEMICALS
6	ETHANOL (ml)	S.D.FINE CHEMICALS

Table 2: List of Chemicals and Equipments used

S.NO	EQUIPMENT NAME	SOURCE
1	DIGITAL WEIGHING MACHINE	SHIMADZU ATY 244
2	UV-VIS DOUBLE BEAM SPECTROPHOTOMETER	ELICO SL 164 DOUBLE BEAM SPECTROPHOTOMETER
3	KESHRY DIFFUSION CELL	ANCHOR, MUMBAI
4	MAGNETIC STIRRER	ERWEKA
5	USP DISSOLUTION APPARATUS	LAB INDIA DS 8000
6	TRAY DRYER	SISCO
7	BATH SONICATOR	WENSAR

METHODOLOGY

Preformulation studies

Pre-formulation testing is the first step in the rationale development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when in combined with excipients. The overall objective of the pre-formulation testing is to generate information

useful to the formulator in developing stable and bio availability dosage forms which can be mass produced.

The goals of pre-formulation studies are

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine its kinetic release rate profile.
- To establish it's compatibility with different excipients.

Hence, preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies.

Characterization of Perindopril

Melting point determination

The melting point of Perindopril was determined by using melting point apparatus.

UV spectroscopy

Preparation of Stock Solution

100 mg of Perindopril was taken in a 100 ml volumetric flask. To that 5 ml of methanol was added and shaken well to dissolve the drug. The solution was made up to the mark with methanol.

- From the above solution 1 ml is diluted to 10 ml with, 7.4 PH phosphate buffer solutions to give 100 µg /ml concentration.
- From the above solution 1 ml is diluted to 10 ml with, 7.4 PH phosphate buffer solutions to give 10 µg /ml concentration.

The prepared solution i.e., 10 µg/ml concentration was scanned for λ_{max} from 200-400 nm in UV/Visible spectrophotometer.

Determination of solubility of Perindopril

The Perindopril is a highly water soluble compound. The solubility was determined in distilled water and phosphate buffer pH 7.4. The procedure can be detailed as follows.

Saturated solution of Perindopril prepared using 10 ml. of distilled water/ phosphate buffer pH 7.4 in 25 ml volumetric flasks in triplicate. Precaution was taken so that the drug remains in medium in excess. Then by using mechanical shaker, the flasks were shaken for 48 hours. The sampling was done on 24th & 48th hour. The sample withdrawn (1 ml after filtration) was diluted with appropriate medium and analyzed by using UV spectrophotometer at 241 nm for phosphate buffer and distilled water respectively.

Fourier Transformation Infra-red (FTIR) analysis

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).The instrument was calibrated by using polystyrene film.

Evaluation of transdermal patches [3, 4, 5]

Physical evaluations

Thickness and weight variation

The thickness of the patch at three different points was determined using thickness gauge and the patches were then weighed individually using digital balance to determine the weight of each patch taken out from the casted film. The patches were subjected to weight variation by individually weighing ten randomly selected patches. Such determinations were carried out for each formulation.

Folding endurance

Using an apparatus designed in laboratory, folding endurance test for films was performed. The disintegration apparatus was modified as a folding endurance apparatus. The apparatus consists of two clamps for holding the film. Out of two clamps, one clamp was fixed while other was moving. The clamps were able to move5cm distance from each other at speed of 30 rpm. The film was attached in such a way that when clamps were at maximum distance the film will be slightly stretched. The apparatus was put on and allowed to run until film broke into two pieces. The folding was counted by rpm.

Percentage Moisture Loss

Accurately weighed films of each formulation were kept in a desiccator and exposed to an atmosphere of 98% relative humidity (containing anhydrous calcium chloride) at room temperature and weighed after 3 days. The test was carried out in triplicate. The percentage of moisture loss was calculated as the difference between initial and final weight with respect to initial weight.

Percentage moisture uptake

Accurately weighed films of each formulation were kept in a desiccator which is maintained at 79.5% relative humidity (saturated solution of aluminium chloride) at room temperature and weighed after 3 days. The test was carried out in triplicate. The

percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

Drug content

Films of specified area were cut and the pieces were taken into a 100 ml volumetric flask containing phosphate buffer (pH 7.4), and the flask was sonicated for 8 h. A blank was prepared in the same manner using a drug-free placebo patch of same dimensions. The solution was then filtered using a 0.45-µm filter and the drug content was analyzed at 241 nm by UV spectrophotometer

In vitro drug release studies

The in-vitro release studies were carried out by using Keshary chein apparatus. The receptor compartment was maintained at 37±1°C by means of a water bath, circulator, and a jacket surrounding the cell. The cells were filled with freshly prepared phosphate buffer pH 7.4. The solution in the receptor compartment was continuously stirred at 60 rpm by means of Teflon coated magnetic stirrer, in order to avoid diffusion layer effects. The Commercial Semi-permeable membrane were mounted between the donor and receptor compartment and secured in place by means of a clamp.

The patch was placed on one side of the semi-permeable membrane. Aliquots of 1ml were removed from the receptor compartment by means of a syringe and replaced immediately with the same volume of buffer solution kept at 37± 1°C. Test samples were taken from the medium at predetermined time intervals over a period of 24 hours and the samples were analyzed for Perindopril content by UV spectrophotometer at 241 nm. The diffusion kinetics of the Perindopril was analyzed by graphical method for zero order, Higuchi and Peppa's exponential equation.

Formulation development

Table 3: Composition of Perindopril Transdermal patches

S.NO	INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)
1	PERINDOPRIL	60	60	60	60	60	60	60	60	60	60	60	60
2	HPMC	300	400	500	---	---	---	---	---	---	250	250	---
3	CARBOPOL 971P	---	---	---	300	400	500	---	---	---	250	---	250
4	EUDRAGIT L100	---	---	---	---	---	---	300	400	500	---	250	250
5	GLYCEROL (4drops)	117.6	117.6	117.6	117.6	117.6	117.6	117.6	117.6	117.6	117.6	117.6	117.6
6	DIBUTYL PHTHALATE (1drop)	27.4	27.4	27.4	27.4	27.4	27.4	27.4	27.4	27.4	27.4	27.4	27.4
7	TWEEN 80 (ml)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
8	ETHANOL	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Preparation of transdermal patches

Transdermal films containing Perindopril were prepared by the solvent evaporation technique for the formulations shown in Table. Solution of polymers were prepared separately in ethanol. The polymeric solutions were mixed to which weighed amount of Perindopril was added slowly. To the mixture, 4 drops of glycerin (117.6 mg), 1 drop of dibutyl phthalate (27.4 mg), and 0.25 ml of surfactant (PEG 400 / Tween 80) and permeation enhancer (DMF / DMSO) were added and mixed. The drug-polymer solution was casted in a glass mould of 40 cm^2 (4x10 cm^2). The mould was kept aside for drying at room temperature for 24 h. Inverted plastic funnel was placed over the mould to prevent the current of air. After drying, the films were peeled from glass mould, wrapped in aluminium foil and preserved in desiccator for further studies.

RESULTS AND DISCUSSION

Fourier Transformation Infra-red (FTIR) analysis

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).The instrument was calibrated by using polystyrene film.

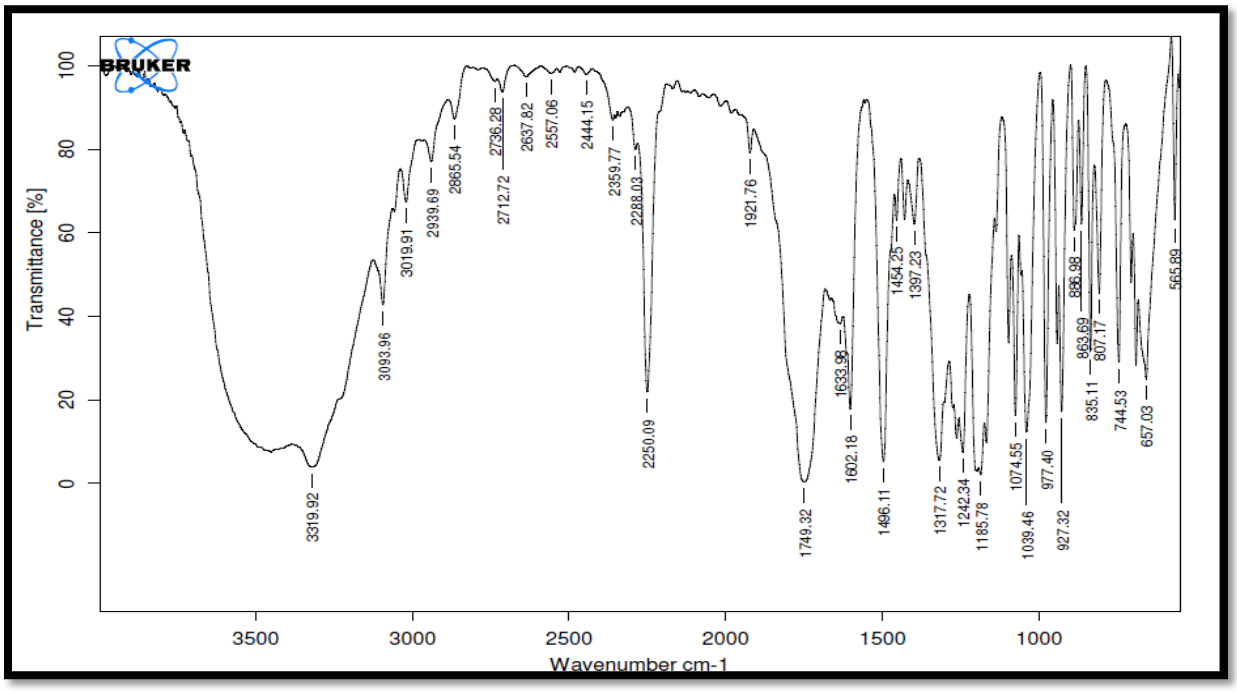

Figure 1: FT-IR Sample for perindopril (pure drug)

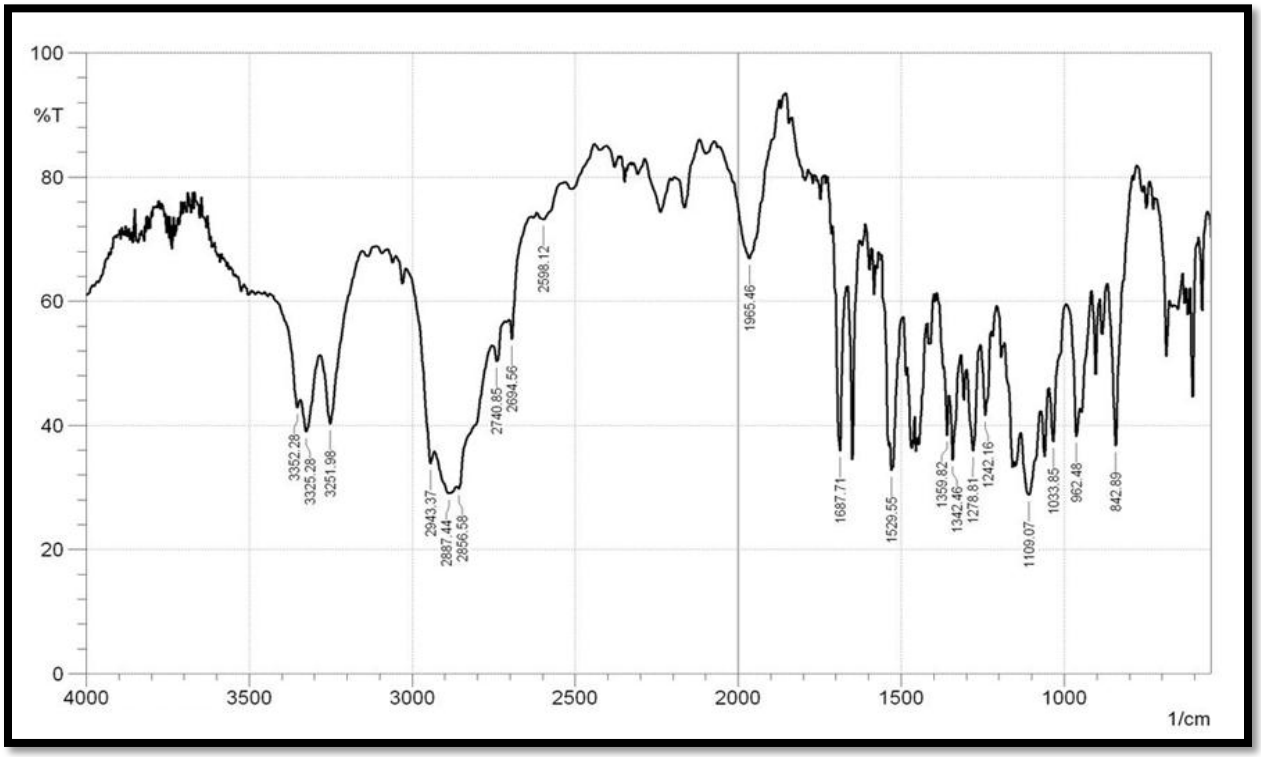

Figure 2 : FT-IR Sample for optimized formulation

Standard calibration curve of perindopril

Table 4: Standard calibration curve of Perindopril

S.NO	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	2	0.116
3	4	0.247
4	6	0.369
5	8	0.492
6	10	0.639

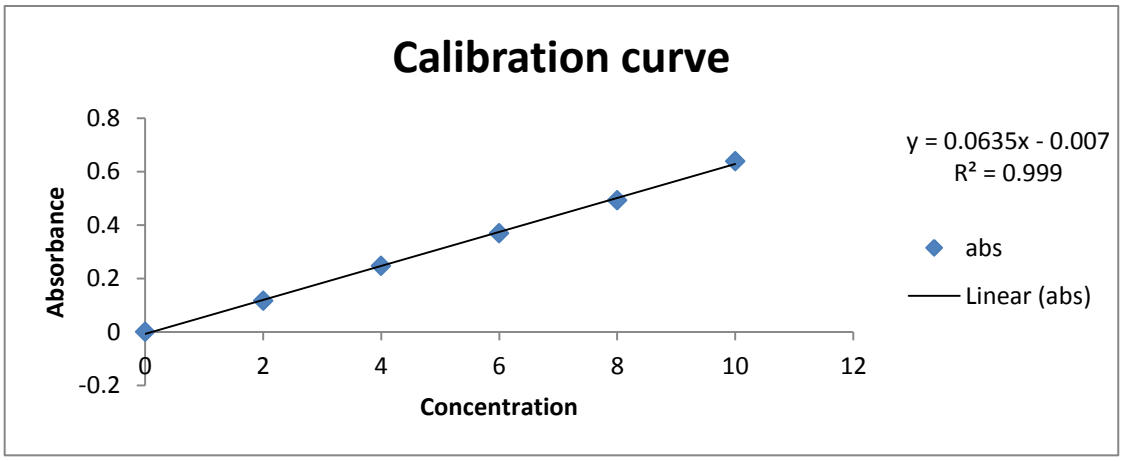

Figure 3: Standard calibration curve of perindopril

Table 5: Release of drug for transdermal patches of perindopril

Time	F1	F2	F3	F4	F5	F-6	F-7	F-8	F-9	F-10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	19.67	17.36	15.67	25.61	22.61	21.57	29.43	26.41	24.61	5.43	12.43	14.56
2	31.91	28.92	25.91	39.56	35.96	32.63	48.54	43.94	40.56	12.12	19.12	25.68
4	43.78	40.93	38.78	58.48	54.38	52.76	76.41	72.94	68.62	23.36	32.36	39.59
6	59.72	56.72	52.72	72.84	68.49	65.46	83.26	81.86	78.83	37.92	47.92	52.49
8	76.38	73.92	69.46	86.38	83.74	81.78	95.49	92.83	89.26	48.92	58.92	67.49
10	87.42	84.47	80.16	93.71	92.82	90.36	100	98.57	95.87	59.21	69.21	76.19
12	93.87	92.59	90.78	100	100	99.57		100	100	68.92	81.92	85.67
24	100	100	99.57			100				84.92	93.72	97.18

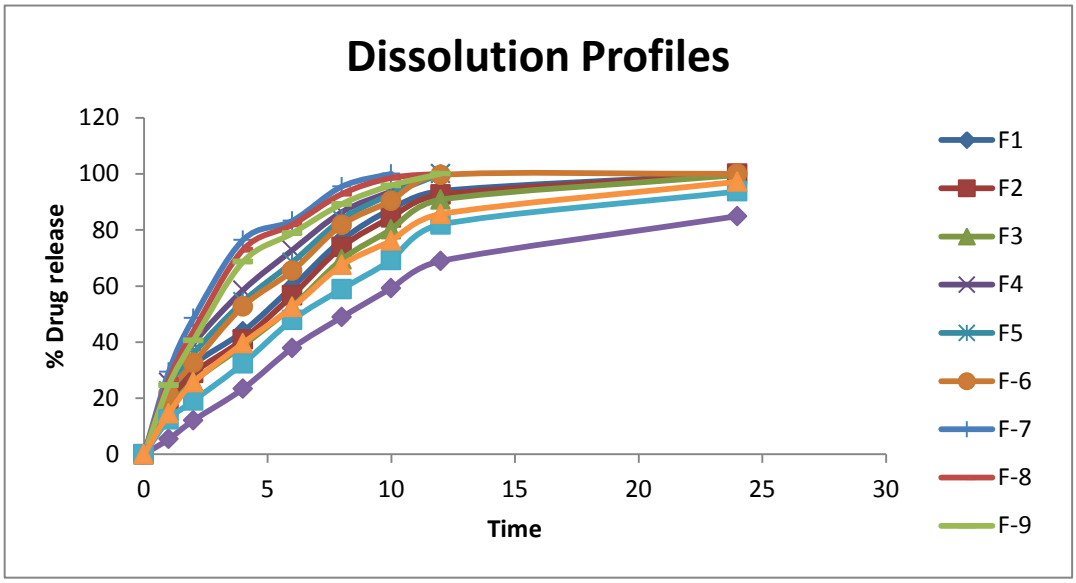

Figure 4: Dissolution profile of perindopril

Kinetic models

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Time	Log T	Square Root Of Time	%Cr	%Drug Remaining	Log %Cr	Log% Drug Retained	Cube Root Of %Drug Remaining
0	0	0	0	100	0	2	4.641589
1	0	1	12.43	87.57	1.094471	1.942355	4.440704
2	0.30103	1.414214	19.12	80.88	1.281488	1.907841	4.324611
4	0.60206	2	32.36	67.64	1.510009	1.830204	4.074439
6	0.778151	2.44949	47.92	52.08	1.680517	1.716671	3.734424
8	0.90309	2.828427	58.92	41.08	1.770263	1.61363	3.450459
10	1	3.162278	69.21	30.79	1.840169	1.48841	3.134271
12	1.079181	3.464102	81.92	18.08	1.91339	1.257198	2.624618
24	1.380211	4.898979	93.72	6.28	1.971832	0.79796	1.844958

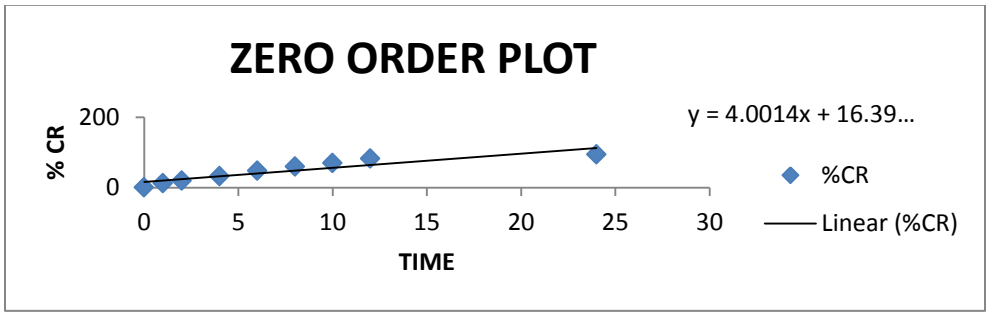

Figure 5: Zero order plot for Optimized formulation

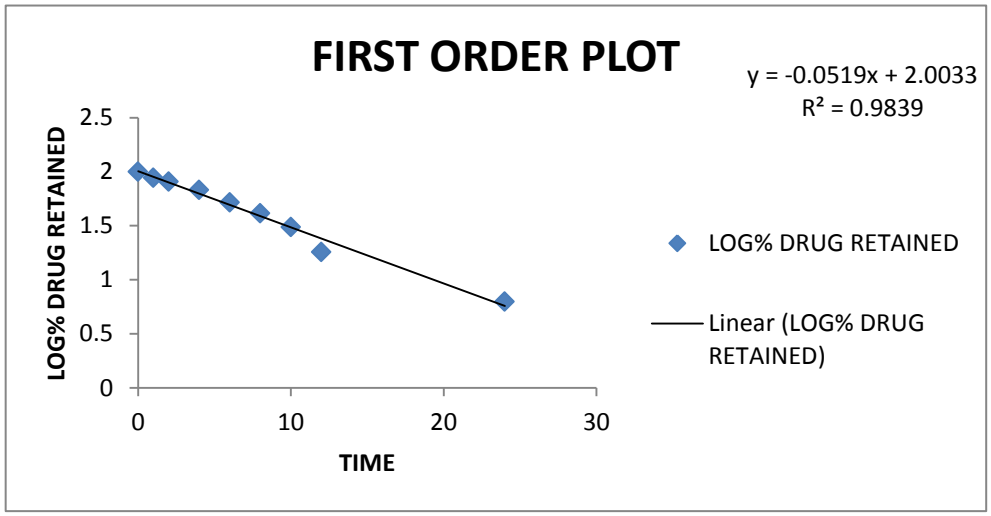

Figure 6: First order plot for Optimized formulation

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-5 after 3 Months. Parameters quantified at various time intervals were shown

Table 6: Stability dissolution profile of F-5 for 1st, 2nd & 3rd months

S.NO.	TIME(Hrs)	F-5 1M	F-5 2M	F-5 3M
1	0	0	0	0
2	1	12.42	12.41	12.39
3	2	19.12	19.10	19.08
4	4	32.35	32.33	32.33
5	6	47.91	47.90	47.90
6	8	58.90	58.89	58.86

7	10	69.20	69.16	69.15
8	12	81.90	81.89	81.86
9	24	93.70	93.67	93.67

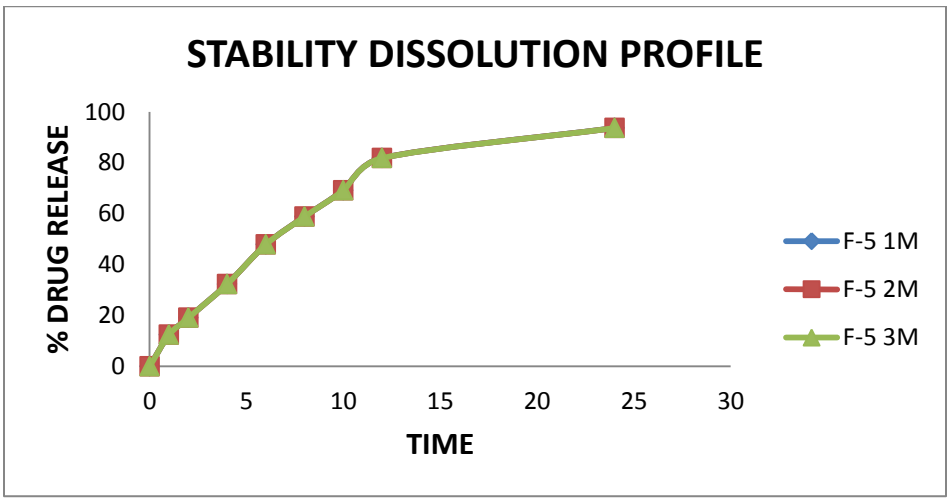

Figure 7: Stability dissolution profile of F-5 for 1st, 2nd & 3rd months

CONCLUSION

In the present work, an attempt has been made to provide transdermal drug delivery using water soluble polymers with Perindopril as the model drug. The main objective of formulating the transdermal system was to prolong the drug release time, reduce the frequency of administration and to improve patient compliance. In the present study five formulations were prepared using single polymer in different ratios, along with plasticizers and penetration enhancer. Finally it was concluded that

- Formulation-7shows formation of brittle patch due to insufficient amount of polymer for patch preparation. So in Formulation-3 an attempt was made by increased quantity of polymer.
- Formulation 1, 2, 4, 5, 6, 8, 9, gave the patch of sufficient strength (% tensile strength) but failed to achieve optimum drug release.
- Formulation 4 has shown better drug release profiles. But the texture of patch is not elegant, so the concentration of plasticizer has increased in formulation.
- Finally, formulation-5 was considered as optimized formula for preparing transdermal patch of Perindopril, where it shown best drug release profile.

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