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Research Article

Formulation and Evaluation of Nifedipine Transdermal Drug Delivery Systems

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ABSTRACT

This study investigates the development of Nifedipine transdermal patches utilizing varying ratios of Hydroxypropyl Methylcellulose K100 (HPMC K100) and Eudragit L100. The formulations were subjected to rigorous evaluation encompassing physicochemical properties, ex vivo permeation studies, and in vitro iontophoresis assessments. The findings indicate that iontophoresis significantly enhanced drug release compared to the chemical method employing Dimethyl Sulfoxide (DMSO) as a penetration enhancer. The transdermal patches exhibited the requisite flux and suitable mechanical properties, suggesting their potential for effective antihypertensive therapy. The combination of HPMC K100 and Eudragit L100 polymers provides a matrix conducive to controlled drug release. The incorporation of PEG as a plasticizer enhances the mechanical properties of the patches, while DMSO and iontophoresis serve as effective permeation enhancers. The iontophoresis technique offers a non-invasive means to augment drug delivery, potentially improving therapeutic outcomes in hypertensive patients.The study successfully developed Nifedipine transdermal patches with optimal physicochemical properties and enhanced drug release profiles. The iontophoresis-enhanced formulations demonstrated superior performance compared to chemical enhancement methods. These findings underscore the potential of iontophoresis in advancing transdermal drug delivery systems for antihypertensive therapy.

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. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. A drug is applied in a

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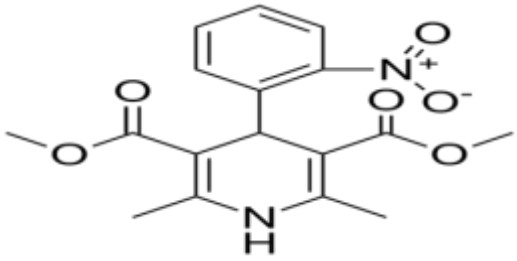
relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the blood stream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.[1]

Materials: Drug Profile

NIFEDIPINE [2-8]:

IUPAC NAME: 3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate



Structure Of Nifedipine

- **Category** : Antihypertensive agent
- **Formula** : $C_{17}H_{18}N_2O_6$
- **Mol. mass** : 346.33g/mol

Mode of action:

Nifedipine decreases arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the influx of calcium ions through L-type calcium channels. Calcium ions entering the cell through these channels bind to calmodulin. Calcium-bound calmodulin then binds to and activates myosin light chain kinase (MLCK). Activated MLCK catalyses the phosphorylation of the regulatory light chain subunit of myosin, a key step in muscle contraction. Signal amplification is achieved by calcium-induced calcium release from the sarcoplasmic reticulum through ryanodine receptors. Inhibition of the initial influx of calcium inhibits the contractile processes of smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased after load. The vasodilatory effects of Nifedipine results in an overall decrease in blood pressure.

EXCIPIENTS PROFILE

- **Polyethylene glycol** [9-11] is a polyether compound.
- **Synonyms:** Polyethylene oxide (PEO), polyoxyethylene (POE), Carbowax
- **Eudragit L 100** [12]: Eudragit L 100 is ammonio methacrylate copolymers consisting of fully polymerized copolymers of acrylic acid esters with 10% of functional quaternary ammonium groups.

Methodology:

Construction of standard calibration curve of Nifedipine

- Construction of standard Calibration curve of Nifedipine in Methanol
- Construction of Standard CCCalibration curve of Nifedipine in Phosphate buffer pH 7.4.

Preparation of Nifedipine Transdermal Films [12-15]

Composition of Nifedipine Transdermal Patches

Formulation code	Drug (mg)	HPMC K100 (mg)	Eudragit L100 (mg)	DMSO (ml)
F1	50	500	-	-
F2	50	350	150	-
F3	50	300	200	-
F4	50	280	220	-
F5	50	260	240	-
F6	50	250	250	-
F7	50	500	-	0.03
F8	50	350	150	0.03
F9	50	300	200	0.03
F10	50	280	220	0.03
F11	50	260	240	0.03
F12	50	250	250	0.03

15% v/w polyethylene glycol - plasticizer.

5% v/w DMSO - penetration enhancer

Each patch 4.9 cm^2contains 3.67 mg of Nifedipine

Characterization of Nifedipine Transdermal Films

Physicochemical properties,Weight variation, Thickness,Folding endurance.Estimation of drug content in polymeric films,Moisture Absorption Studies,Moisture Content Determination of Mechanical properties, *Ex-vivo* Permeation Studies and *In vitro* release studies through Iontophoresis:

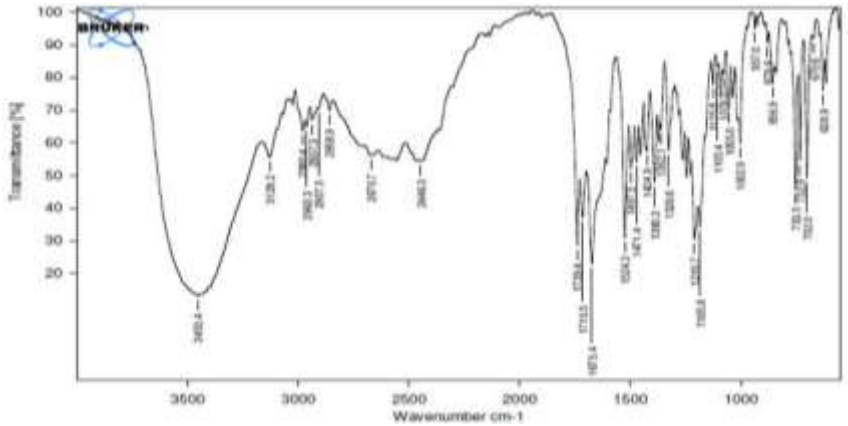
RESULTS AND DISCUSSIONS

Pre-formulation study:

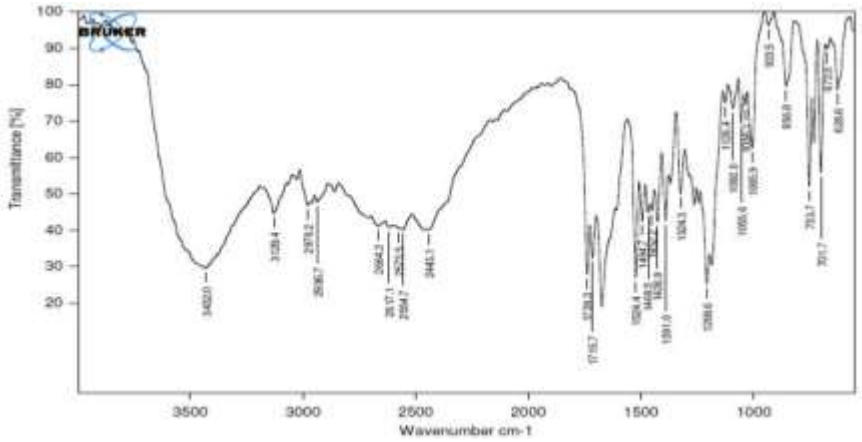
Preformulation studies are primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients.

FTIR Compatibility Studies:

In the FTIR spectra of pure drug and formulation with other ingredients (different polymers) it is observed that the peaks of major functional groups of Nifedipine, which are present in spectrum of pure drug are observed. It means there are no interactions between drug and other ingredients in a physical mixture and drug is compatible with other ingredients.



FTIR spectra of Nifedipine



FTIR spectra of Nifedipine and Excipients

Construction of Calibration Curve of Nifedipine

Standard Calibration Curve of Nifedipine in methanol

Concentration(µg/ml)	Absorbance
0	0
10	0.241
20	0.521
30	0.811
40	1.112
50	1.328

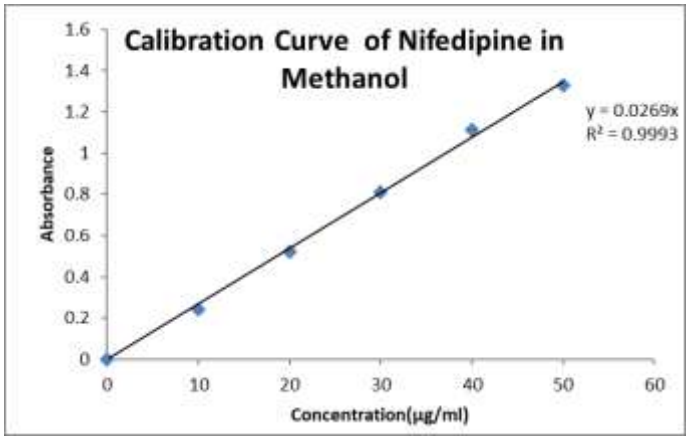
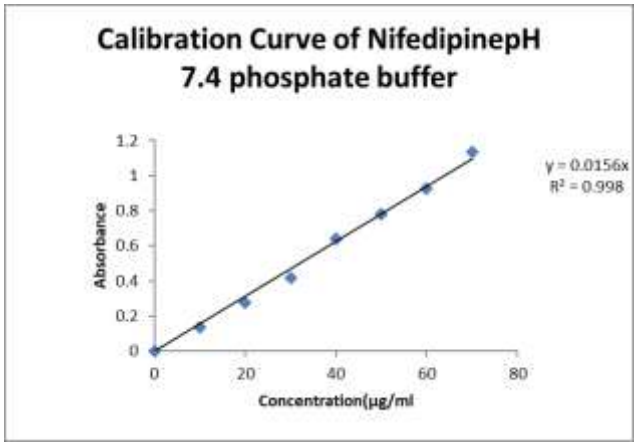


Fig: Standard Calibration Curve of Nifedipine in Methanol

Standard Calibration Curve of Nifedipine pH 7.4 phosphate buffer

Concentration(µg/ml)	Absorbance
0	0
10	0.134
20	0.278
30	0.415
40	0.642
50	0.781
60	0.924
70	0.965



Standard gr Calibration Curve of Nifedipine in pH 7.4 phosphate buffer

Weight variation, thickness and folding endurance of Nifedipine transdermal patches

Formulation	Weight variation (mg)	Thickness (mm)	Folding endurance
F1	48.02±1.8	0.826±0.263	564.61±0.576
F2	34.87±1.24	1.306±0.223	437.28±1.426
F3	39.37±0.86	0.986±0.233	491.73±0.796
F4	43.52±1.53	0.866±0.243	552.93±0.976
F5	46.86±1.05	0.596±0.253	561.14±0.926
F6	33.48±0.76	1.576±0.203	434.64±0.686
F7	48.66±0.82	0.706±0.273	569.08±1.336
F8	36.56±1.39	1.016±0.213	456.26±1.066
F9	40.73±1.7	1.416±0.223	492.86±0.786
F10	41.89±1.16	1.296±0.253	560.73±0.666
F11	44.62±1.22	0.616±0.263	565.62±1.186
F12	34.36±0.94	0.666±0.223	472.95±1.136

Drug content, % Moisture absorbed, %Moisture content of Nifedipine transdermal patches

Formulation	Drug content (mg)	%Moisture absorbed	%Moisture Content
F1	2.38±0.99	11.23±1.5	9.76±0.88
F2	2.95±1.32	8.39±1.66	4.95±0.88
F3	2.18±0.87	10.23±0.88	7.3±1.2
F4	2.39±1.21	7.95±1.5	9.78±1.35
F5	2.42±1.07	11.01±0.87	9.78±1.88
F6	2.85±0.58	7.99±1.28	5.01±0.8
F7	2.55±1.3	13.01±1.07	9.78±0.86
F8	3.12±0.95	7.91±0.72	6.64±0.58
F9	2.29±0.78	8.23±0.68	6.75±0.81
F10	2.35±1.58	9.91±0.52	8.98±0.85
F11	2.41±1.3	11.03±1.22	9.55±0.86
F12	2.89±0.89	8.01±1.47	7.31±1.9

Mechanical properties of optimized formulations

Formulation code	Tensile strength(kg/m^2)	Elongation at break ($\%mm^2$)
F4	1.31±0.15	25.31±0.34
F9	0.79±0.39	40.46±0.98
F10	1.50±0.84	22.46±0.87

Permeation Studies of Nifedipine from transdermal patches

Time	Cumulative amount of drug permeated (µg/cm^2)			
(h)	F1	F2	F3	F4
0	0	0	0	0
1	225.856±7.9	230.61±6.415	242.04±8.84	269.57±0.471
2	248.566±10.3	4490.21±0.415	482.5±1.1	403.61±6.471
3	447.94610.3	601.93±2.255	482.7±9.32	483.99±8.271
4	622.906±11.7	669.77±6.855	602.72±2.88	641.81±8.871
5	803.606±7.96	867.93±0.235	846.04±9.04	842.19±6.471
6	868.166±12.76	6.41±8.475	44.12±9.24	44.39±8.891
7	1162.946±17.94	204.57±0.415	208.06±9.04	242.23±8.311
8	1268.566±19.94	409.99±2.235	408.46±7.04	445.57±2.531
9	1414.346±14.16	670.37±2.415	628.64±1.04	664.17±4.471
10	1688.546±10.34	866.19±0.415	822.06±6.86	2001.81±8.551
12	1809.966±13.58	2046.57±4.415	2244.12±0.84	2243.83±2.091
24	2247.946±19.94	2422.39±8.215	2646.28±8.64	2895.19±4.271
Flux J_{ss}	26.066±2.54	29.53±0.905	30.53±1.33	33.36±1.421

Permeation of Nifedipine from transdermal patches

Time	Cumulative amount of drug permeated (µg/cm^2)			
(h)	F5	F6	F7	F8
0	0	0	0	0
1	199.61±5.564	260.75±7.547	292.7±12.446	502.64±6.014
2	320.72±3.864	347.73±6.607	446.47±5.576	610.22±7.594
3	453.95±9.264	555.82±5.927	570.15±3.866	769.87±10.514
4	564.04±4.564	750.33±2.617	728.33±9.566	942.87±8.644
5	714.51±12.564	927.59±7.677	866.68±7.346	1059.8±9.404
6	888.1±10.564	1087.97±7.587	1081.75±7.886	1228.62±6.644
7	1081.51±3.664	1279.91±10.597	1274.05±5.346	1395.23±11.514
8	1260.24±4.764	1438.82±3.067	1489.12±2.726	1529.56±4.894
9	1453.28±8.564	1613.88±5.007	1691.67±4.766	1682.6±13.614
10	1656.6±2.564	1836.65±9.827	1818.32±8.396	1940.6±2.794
12	1907.26±3.964	2066.39±12.907	2065.27±6.746	2208.51±8.994
24	2240.78±6.764	2439.47±8.417	2599.31±10.546	2697.19±7.794
Flux J_{ss}	26.9±0.914	29.97±0.737	30.82±1.586	32.78±1.224

Permeation Studies of Nifedipine from transdermal patches

Time	Cumulative amount of drug permeated (µg/cm^2)			
(h)	F9	F10	F11	F12
0	0	0	0	0
1	423.68±7.27	278.03±4.215	244.77±10.551	336.52±9.23
2	531.21±12.06	449.42±10.565	309.07±2.871	468.64±5.65
3	616.72±14.14	640.26±7.945	544.61±6.841	567.73±10.25
4	779.67±10.11	823.76±2.965	658.38±4.801	725.54±3.1
5	931.24±11.23	998.81±8.535	850.32±9.581	921.51±5.36
6	1144.1±4.83	1222.68±3.795	1055.75±13.891	1127.25±6.32
7	1364.3±6.14	1407.28±6.465	1295.85±12.561	1333.55±7.79
8	1568.72±6.91	1587.08±12.575	1520.15±9.571	1550.85±9.01
9	1777.91±9.98	1776.78±9.715	1698.05±10.251	1730.15±9.84
10	1988.2±11.01	1988.78±10.705	1863.15±8.961	1963.85±3.88
12	2286.57±7.91	2360.38±5.395	2023.05±6.541	2254.15±12.12

24	2965.17±3.7	3229.38±6.755	2412.75±9.271	2601.85±11.62
Flux J_{ss}	33.23±1.02	35.08±0.985	29.69±1.301	31.65±1.85

Permeation of Nifedipine from transdermal patches using iontophoresis (F1i to F6i)

Time	**Cumulative amount of drug permeated(µg/cm²)**		
(h)	**F1i**	**F2i**	**F3i**
0	0	0	0
1	377.87±5.725	450.81±12.407	478.47±8.828
2	637.69±15.745	756.88±4.637	781.98±7.748
3	892.86±6.595	1035.27±10.397	1080.15±3.648
4	1191.78±9.375	1337.77±7.947	1374.95±9.888
5	1373.08±10.585	1522.77±9.817	1533.85±10.318
6	1585.98±8.815	1711.07±12.657	1799.65±5.648
7	1781.58±7.575	1912.87±10.797	1993.45±2.898
8	1951.18±12.355	2122.07±9.007	2242.95±13.548
9	2129.08±10.975	2287.27±7.517	2429.75±12.668
10	2254.98±9.245	2439.77±6.297	2593.45±5.048
12	2413.88±8.485	2629.67±6.657	2815.45±11.348
24	2757.78±14.545	3076.47±8.617	3247.75±8.918
Flux J_{ss}	36.82±1.445	40.54±0.607	42.08±1.038

Permeation of Nifedipine from transdermal patches

Time	**Cumulative amount of drug permeated (µg/cm2)**		
(h)	**F4i**	**F5i**	**F6i**
0	0	0	0
1	604.55±6.517	328.13±7.855	410.34±9.727
2	963.11±10.617	592.37±4.695	662.48±4.617
3	1229.97±14.587	854.04±9.585	964.51±13.517
4	1531.37±11.187	1112.4±8.975	1178.47±2.517
5	1846.47±7.357	1260.6±6.525	1402.67±5.957
6	2015.87±5.557	1406.6±5.365	1583.57±7.707
7	2161.77±9.647	1572.1±2.905	1777.57±8.987
8	2405.07±8.607	1725.4±6.255	1993.97±10.897
9	2618.67±8.287	1938±10.685	2177.07±12.537
10	2773.07±5.957	2072.3±9.795	2329.67±5.667
12	2984.17±12.447	2282.2±8.355	2552.37±11.477
24	3571.37±9.887	2687.9±7.555	3027.67±12.597
Flux J_{ss}	46.03±0.797	34.3±1.315	38.85±0.987

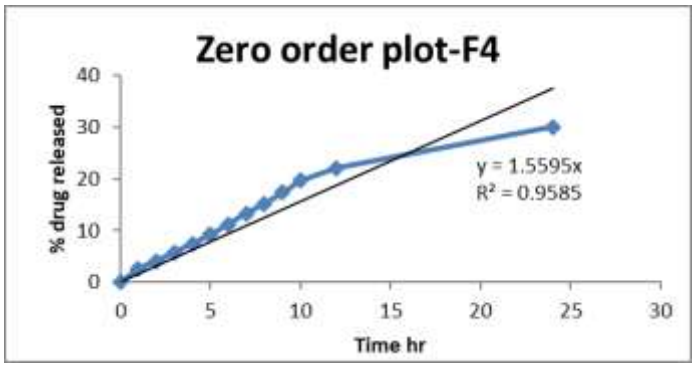
Comparative study of Nifedipine permeation

Time	**Cumulative amount of drug permeated (µg/cm²)**		
(h)	**F4**	**F10**	**F4i**
0	0	0	0
1	270.7±11.18	277.62±4.87	604.66±6.519
2	413.83±8.18	449.01±11.22	963.22±10.619
3	585.22±9.98	639.85±8.6	1230.02±14.589
4	752.93±9.58	823.35±3.62	1531.48±11.189
5	942.31±8.18	998.4±9.19	1846.58±7.359
6	1144.99±10.6	1222.37±4.45	2015.98±5.559
7	1353.29±10.03	1406.37±7.12	2161.88±9.649
8	1547.39±14.24	1586.67±13.23	2405.48±8.609

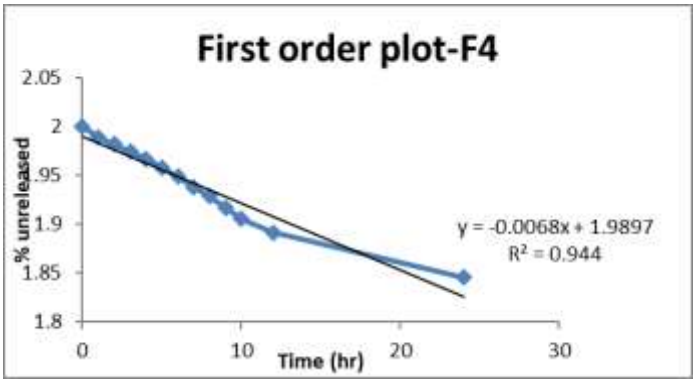
9	1774.79±15.18	1776.97±10.37	2618.78±8.289
10	2003.19±10.26	1988.67±11.36	2773.18±5.959
12	2254.39±12.8	2359.97±6.05	2984.28±12.449
24	3063.99±14.88	3229.07±7.41	3571.08±9.889
Flux J_{ss}	34.51±2.04	34.67±1.64	46.14±0.799

Time	**Cumulative amount of drug permeated (µg/cm²)**		
(h)	**F4**	**F10**	**F4i**
0	0	0	0
1	2.646	2.7146	5.9192
2	4.0474	4.4002	9.4374
3	5.733	6.2622	12.054
4	7.3696	8.0654	15.0038
5	9.2316	9.7804	18.0908
6	11.2112	11.9854	19.747
7	13.2594	13.7788	21.1778
8	15.1606	15.5428	23.569
9	17.3852	17.4048	25.6564
10	19.6294	19.4824	27.1754
12	22.0892	23.1182	29.2432
24	30.0174	31.6442	34.9958

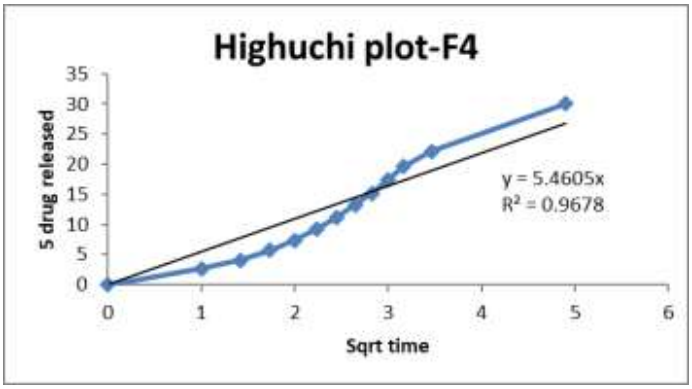
Zero order plot-F4, b- first order plot-F4, C- Higuchi plot-F4



Zero order plot-F4

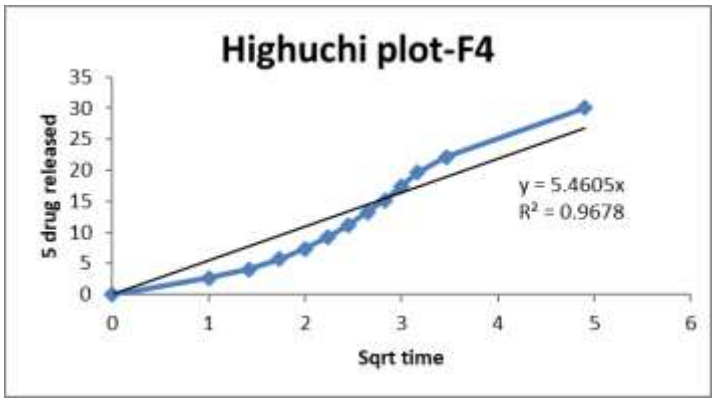


First order plot-F4

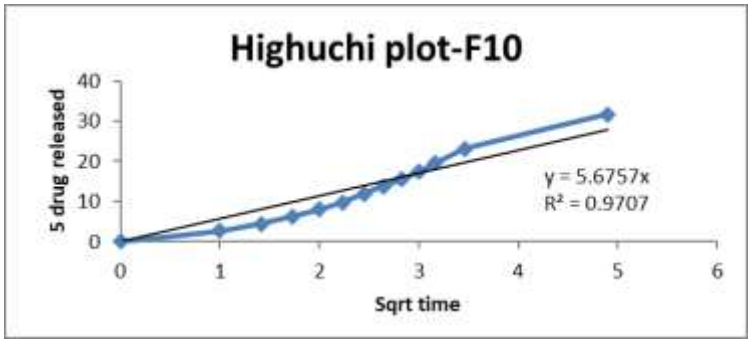


Higuchi plot-F4

Zero order plot-F10, b- first order plot-10, C- Higuchi plot-10

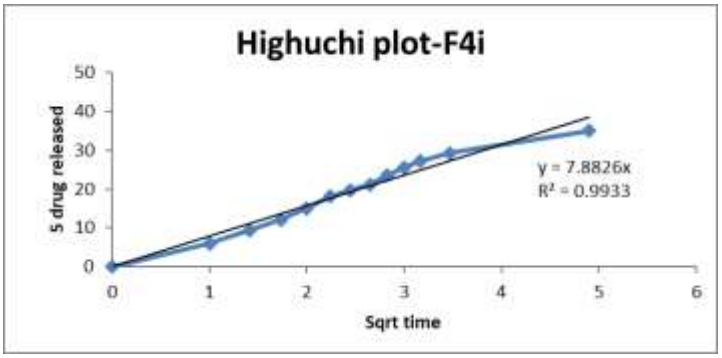


Zero order plot-F10



Higuchi plot-F 10

Zero order plot-F4i



Higuchi plot-4i

Development of Nifedipine Transdermal Films

The ex vivo permeation studies conducted on rat abdominal skin using Nifedipine-loaded transdermal patches have provided valuable insights into the factors influencing drug delivery. Formulations containing HPMC K100 and Eudragit L100F4 and F10 exhibited the highest cumulative drug permeation over 24 hours, with values of 3232.38 ± 6.755 µg/cm² and 2895.19 ± 4.271 µg/cm², respectively. These formulations demonstrated a significant increase in drug flux compared to others, indicating the importance of polymer composition in enhancing skin penetration. Increasing the HPMC concentration in these formulations further enhanced drug penetration, suggesting that HPMC plays a crucial role in improving skin permeation. However, despite the increased permeation, the required flux was not achieved with these compositions, highlighting the need for additional strategies to enhance drug delivery. The inclusion of Dimethyl Sulfoxide (DMSO) as a penetration enhancer in formulations F7 to F12 significantly improved the ex vivo skin permeation of Nifedipine. DMSO is known for its ability to disrupt the stratum corneum, facilitating enhanced drug diffusion through the skin barrier. Iontophoresis was conducted for 2 hours at a current of 0.5 mA, followed by 24 hours of passive diffusion.Iontophoresis facilitates drug transport through the skin by applying a low electrical current, which enhances the movement of charged drug molecules via electrorepulsion and electroosmosis. This technique has been shown to significantly increase the transdermal delivery of various drugs, including Nifedipine he successful permeation of Nifedipine through rat abdominal skin suggests that similar formulations may be effective for human skin, considering the similarities between rat and human skin permeability profiles. However, further studies are necessary to confirm the efficacy and safety of these formulations in human subjects. The combination of optimized polymer matrices, penetration enhancers like DMSO, and iontophoresis presents a promising approach to enhance the transdermal delivery of Nifedipine. These strategies not only improve drug permeation but also ensure that the required therapeutic flux is achieved, paving the way for the development of effective transdermal therapeutic systems for Nifedipine.

CONCLUSION:

In the present study, an attempt was made to formulate an anti-hypertensive drug Nifedipine in the form of transdermal patches using different ratios of HPMC K100 and Eudragit L100. These were evaluated for physico-chemical properties, *ex vivo* permeation and *in vitro* iontophoresis studies and were found to meet the required flux. From the results obtained, iontophoresis enhanced the drug release from the Nifedipine transdermal patches

compared with the chemical method using penetration enhancer DMSO. The transdermal patches of Nifedipine with required flux could be prepared with suitable mechanical properties; further studies are recommended to find their therapeutic utility in humans by pharmacokinetic and pharmacodynamic studies.

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