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Original Article

Preparation of Transdermal Films of Nifedipine: *Ex-vivo* and *In-vitro* Studies

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ABSTRACT

Objective: The aim of present study was to prepare and evaluate the transdermal films (TFs) of Nifedipine (NFDP). **Methods:** The TFs were prepared by solvent evaporation technique and twelve formulations of NFDPTFs were prepared by taking HPMC E15 and Eudragit L100 in different ratios. Polyethylene glycol (15%) and Dimethyl sulfoxide (DMSO) were incorporated as plasticizer and permeation enhancer respectively. DMSO was incorporated in the formulations F7-F12 but it was absent in F1-F6. **Results:** The prepared TFs were evaluated for weight variation, thickness, folding endurance, drug content, moisture absorption, moisture content determination, mechanical properties and *ex-vivo* permeation. Mechanical properties revealed that the formulations F4 and F10 were found to be strong enough but not brittle. Hence, the formulations F4 and F10 were selected for *ex-vivo* studies. The formulations F4 and F10 showed maximum drug permeation within 24 h and formulation with permeation enhancer showed highest drug permeation than formulation without permeation enhancer. **Conclusion:** It could be concluded that the formulation with permeation enhancer (F10) showed highest permeability through the rat skin than formulation without permeation enhancer.

Key words: Matrix films, NFDP, DMSO, *In-vitro* studies, *Ex-vivo* studies.

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INTRODUCTION

Conventional systems of medication that require multi dose therapy are having many problems. The controlled drug delivery is a newer approach to deliver drug into systemic circulation at a predetermined rate. Our system should duplicate continuous intravenous infusion, which not only bypasses the hepatic first pass elimination but also maintains a constant, prolonged and therapeutically effective drug level in the body.[1-2] This is made possible by using intact skin as a part of drug administration to provide continuous delivery of drug into the systemic circulation. The drug molecules are then transported to the target site, which could be relatively remote from the site of administration, to produce therapeutic action.[3] NFDP is a calcium channel blocker with vasodilatory properties due to the enhancement of endothelial nitric oxide release, which causes relaxation of vascular smooth muscle. It is used in the treatment of hypertension by decreasing heart rate and myocardial contractility. NFDP also inhibits platelet aggregation, suppression of renin activity, reduction of tonic sympathetic outflow to the periphery from cerebral vasomotor centres and decreased peripheral vascular resistance. NFDP is rapidly absorbed from the gastrointestinal tract and is subjected to an extensive first pass effect; thereby the bioavailability will be decreased. NFDP undergoes extensive metabolism in which less than 0.5% of the unchanged drug appears in the urine. NFDP is about 98% plasma protein bound, mostly to albumin shown in *In-vitro* studies. In order to avoid the first pass metabolism of NFDP, the transdermal drug delivery is preferred.[4-5]

Polymers like HPMC family are good thickeners as well as matrix forming agents.[6] Eudragits are also good film forming agents and they are the best choice for the preparation of sustained release dosage forms.[7]

The aim of present study was to prepare matrix type TFs containing NFDP by solvent evaporation technique, using different ratios of HPMC E15 and Eudragit L100 for controlled release of drug. Polyethylene glycol (15%) was incorporated as plasticizer in all the formulations. DMSO (5%) was used as a penetration enhancer and incorporated in the formulations F7-F12.

MATERIALS AND METHODS

Materials

NFDP was a gift sample from Aurobindo Pharma Ltd., INDIA and other ingredients such as HPMC E15 and Eudragit L100 from Qualikem Fine Chemicals Ltd., INDIA, Polyethylene glycol and Dialysis membrane from Finar Chemicals Ltd., INDIA and remaining chemicals used were of analytical grade.

Preparation of NFDPTFs

Matrix type NFDPTFs were prepared by solvent evaporation technique[8] using different ratios of HPMC E15 and Eudragit L100. The polymers were weighed in requisite ratios and allowed for swelling for about 6 h in solvent mixture (1:1 ratio of methanol and chloroform) and 15% v/w Polyethylene glycol was incorporated as plasticizer. Then the drug solution was added to the polymeric solution, casted on to an umbra petriplate of surface area about 66.44 cm^2. Then the formulations are allowed for air drying for overnight which followed by vacuum drying for 8-10 h. The entire sheet was cut into small patches with an area of 4.9 cm^2 i.e. with a diameter of 2.5 cm and each patch contains 3.67 mg of drug. About 13 patches were obtained from each sheet. Formulations F1 to F6 composed of HPMC E15 and Eudragit L100 in different ratios. Formulations F7 to F12 were of same composition as the above but penetration enhancer DMSO (5% v/w) was incorporated. All formulations contained 15% v/w polyethylene glycol as plasticizer.

Evaluation of NFDPTFs

NFDPTFs were evaluated for thickness using screw gauge (*Mitutoyo* Co., Japan), weight variation,[9] folding endurance determined manually, drug

content estimated at 338 nm using UV-Visible spectrophotometer (Lab INDIA 1700 UV-Visible spectrophotometer, INDIA),[10] moisture absorption[11] and moisture content using desiccator,[8] mechanical properties using a microprocessor based advanced force gauze (Ultra Test, Mecmesin, UK) equipped with a 25 kg load cell,[11] and *Ex-vivo* permeation of drug through rat skin.[12,13]

Statistical analysis

One-way and two-way ANOVA was applied as the test of tool using Graph Pad Prism 6 and significance was set at $p<0.05$. The results were expressed as mean ± standard deviation (SD).

RESULTS AND DISCUSSION

NFDPTFs were prepared by solvent evaporation technique. Films were formulated with HPMC E15, Eudragit L100 and many experiments were performed by varying the amount of the polymers. Initially, the experiment was initiated by taking 0.2 gm of polymer and as the polymer concentration increased the film could accommodate more amount of NFDP. Precipitation of the drug was predominant with 0.2 gm of polymer and as the polymer amount was increased to 0.5 gm, the precipitation decreased. Still increase in polymer concentration to 0.6gm observed no precipitation and the films were flexible. Therefore, the maximum amount of polymer taken was 0.6 gm. In addition, experiments were conducted to know optimal concentration of plasticizer to be used in all kinds of films. Plasticizer at concentration of ≤5% v/w of film former was insufficient to form films. Plasticizer concentration at 5-10% v/w yielded hard and inflexible films. Further, increasing the concentration of plasticizer above 20% v/w resulted in enormous increase in drying time. Therefore, the films were prepared using 15% v/w of plasticizer and the prepared films were strong enough but not brittle. Films (F7-F12) were also contained DMSO as penetration enhancer to increase the penetrability through the skin.

Characterization of NFDPTFs

The prepared films were evaluated for the properties such as weight variation, thickness, folding endurance, estimation of drug content, moisture absorption, moisture content determination, measurement of mechanical properties, *Ex-vivo* permeation studies, *In-vitro* release studies using iontophoresis and results were reported in Table 2-3. Results of weight variation test indicated uniformity in weight of films, as evidenced by SD values, which were less than 2.0 for all formulations and it was ranged from 32.37 ± 0.49 mg for formulation F6 (HPMC E15 and Eudragit L100) to 46.9 ± 1.53 for F1 (HPMC E15). The weight increased with increase in the hydrophilic polymer concentration. In thickness variation test, the thickness was found to be uniform and it was increased with increase in polymer concentration. The SD values were less than 2 for all the formulations, an indication of more uniform films and varied from 0.19 ± 1.54 mm for F6 to 0.26 ± 0.67 mm for F7. The folding endurance measures the ability of film to withstand rupture and its strength. The folding endurance of HPMC E15 containing films has in the range of 562 to 566 and combination of HPMC E15 and Eudragit L100 containing films has in the range of 432 to 563. The folding endurance number gives the mechanical property of the films, high folding endurance number indicates that possessing the good mechanical property. The folding endurance number was increased with increase in polymer content. These results indicated that the films would not break and would maintain their integrity with general skin folding when applied. Good uniformity in drug content was observed in all TFs as evidenced by low SD values. The drug content was ranged from 2.73 ± 0.55 mg in formulation F6 (HPMC E15 & Eudragit L100) to 3.42 ± 1.37 mg in formulation F7 (HPMC E15). The drug content was maximum in the formulation containing more amount of hydrophilic polymer. Formulation F6 showed minimum drug content (2.73 ± 0.55) which might be due to the improper solubility of drug in polymeric solution or uneven distribution of drug in films and formulation F7 showed maximum drug content (3.35 ± 0.96). Results from drug content analysis revealed that the method used to prepare the films in this study was capable of giving minimum batch variability and uniform drug content. The moisture content in the films was ranged from 4.58 ± 0.77% for F6 (HPMC E15 & Eudragit L100) to 9.35 ± 0.94% for formulation F7 with HPMC E15. The moisture absorption in the formulations was ranged from 6.42 ± 1.25% for F6 (HPMC E15 & Eudragit L100) to 11.44 ± 1.03% for F7 (HPMC E15). The results revealed that the moisture absorption and moisture contents were found to be increased with increase in the concentration of hydrophilic polymer (HPMC E15) but it is vice versa in case of the polymer Eudragit L100. The small moisture content in the formulations can help them to remain stable and from being a completely dried and brittle film. Tensile strength gives a nature of films such as strength and elasticity. Low tensile strength indicates a soft and weak polymer; moderate tensile strength offers a soft and tough polymer or a hard and brittle polymer; whereas high tensile strength gives a hard and tough polymer. It is suggested that a good film should possess relatively high tensile strength. Observations from the tensile strength and elongation studies indicate that the formulations F4 and F10 were found to be strong and flexible but not brittle. Hence, those were selected for further studies. *Ex-vivo* permeation studies of films gave the results of *In-vitro* NFDP permeation through the rat skin. The formulation F4 among the formulations F1-F6 (which do not have permeation enhancer, DMSO) exhibited the maximum (3062.63 µg) cumulative amount of drug permeation in 24 h with the flux of 32.82. Formulations consist of HPMC E15 only couldn't permeate the maximum amount of drug through the rat skin. In another study, formulation with DMSO (F10) showed good drug permeability (3227.78 ± 6.74 µg) in *Ex-vivo studies*. It was observed from significant studies, F10 showed significant drug permeation ($p<0.05$) though the rat skin than F4. Drug release from the films depends on the chemical properties of the drug and nature of the formulation as well as physicochemical and physiological nature of the biological membrane. In the present investigation, different formulations exhibited variable amounts of drug release through the rat skin in *Ex-vivo* studies. It was found that the formulation F4 and F10 released the drug for 24 h and it indicates that the film can be applied once in a day. Therefore, rate controlling membranes of Eudragit L100 were cast with an aim to achieve controlled release of NFDP from the drug reservoir of

Table 1: Composition of NFDP Transdermal Patches

Formulation	Drug (mg)	HPMC E15 (mg)	Eudragit L100 (mg)	DMSO (ml)
F1	50	600	-	-
F2	50	400	200	-
F3	50	450	150	-
F4	50	500	100	-
F5	50	550	50	-
F6	50	350	250	-
F7	50	600	-	0.03
F8	50	400	200	0.03
F9	50	450	150	0.03
F10	50	500	100	0.03
F11	50	550	50	0.03
F12	50	350	250	0.03

Table 2: Weight variation, thickness, folding endurance, drug content, % Moisture absorbed, %Moisture content of NFDPTFs.

Formulation	Weight variation (mg)	Thickness (mm)	Folding endurance	Drug content (mg)	%Moisture absorbed	%Moisture Content
F1	46.9±1.53	0.25±0.79	562.45±0.53	3.35±0.96	10.87±1.58	9.34±0.96
F2	33.76±0.97	0.2±1.27	435.12±1.38	2.83±1.29	7.92±1.82	4.62±0.85
F3	38.26±0.59	0.22±0.95	489.57±0.75	3.05±0.84	9.67±0.95	5.97±1.17
F4	42.41±1.26	0.23±0.83	550.77±0.93	3.26±1.18	8.39±1.46	8.35 ±1.32
F5	45.75±0.78	0.24±0.56	558.98±0.88	3.29±1.04	10.45±0.93	8.45±1.95
F6	32.37±0.49	0.19±1.54	432.48±0.64	2.73±0.55	6.42±1.25	4.58±0.77
F7	47.55±0.55	0.26±0.67	566.92±1.29	3.42±1.37	11.44±1.03	9.35±0.94
F8	35.45±1.12	0.205±0.98	454.1±1.02	2.99±0.92	8.35±0.89	5.21±0.55
F9	39.62±1.43	0.21±1.38	490.7±0.74	3.16±0.75	8.86±0.64	6.32±0.79
F10	40.78±0.89	0.24±1.26	558.57±0.62	3.32±1.55	9.34±0.59	7.56±0.82
F11	43.51±0.95	0.25±0.58	563.46±1.14	3.38±1.27	10.48±1.19	9.12±0.93
F12	33.25±0.67	0.215±0.63	470.79±1.09	2.76±0.86	6.54±1.53	5.89±1.87

Results were expressed in mean ± SD (n=3)

Table 3: Permeability and mechanical properties of formulation F4 and F10

Time (h)	Cumulative amount of drug permeated (µg/cm2)		Mechanical properties	
	F4	F10	Tensile strength (kg/m2)	Elongation at break (%mm-2)
0	0	0	F4	F4
1	269.01±10.5	276.35±4.20	1.38±0.58	24.92±1.42
2	412.14±7.50	447.74±10.55	F10	F10
3	583.53±9.30	638.58±7.93	1.46±0.78	22.53±0.98
4	751.24±8.90	822.08±2.95		
5	940.62±7.50	997.13±8.52		
6	1143.93±9.92	1221±3.78		
7	1351.66±9.35	1405.61±6.45		
8	1545.07±13.56	1585.4±12.56		
9	1773.71±14.50	1775.17±9.70		
10	2001.25±9.58	1987.14±10.69		
12	2252.27±12.12	2358.7±5.38		
24	3062.63±14.20	3227.78±6.74		
Flux Jss	32.82±1.36	33.4± 0.97		

Results were expressed in mean ± SD (n=3)

HPMC. It was observed that the formulations containing permeability enhancer DMSO showed improvement in the drug permeability across the rat skin.

CONCLUSION

It could be concluded from the results that the formulations F4 and F10 were considered as the best formulations supported by *Ex-vivo* studies and also it was observed that the formulation with permeation enhancer (F10) showed highest permeability through the rat skin than formulation without permeation enhancer. In this context, further study is recommended in support of its efficacy claims and improved NFDP bioavailability studies on human beings.

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Nil

CONFLICTS OF INTEREST

Authors declared that there are no conflicts of interests.

ABBREVIATION USED

TFs: Transdermal films; **NFDP:** Nifedipine; **HPMC:** Hydroxy Propyl Methyl Cellulose; **DMSO:** Dimethyl sulfoxide; **SD:** Standard Deviation.

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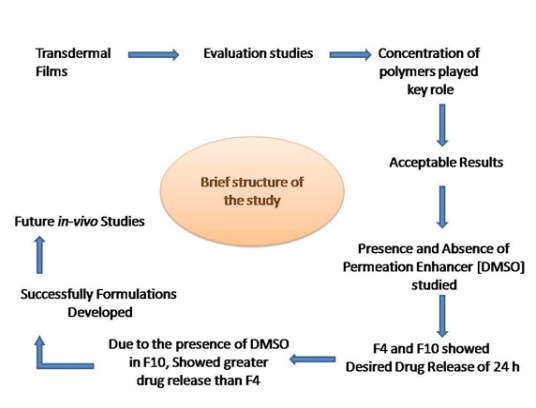
PICTORIAL ABSTRACT



SUMMARY

- Transdermal films of Nifedipine were successfully prepared by taking different ratios of polymers like HPMC and Eudragit families.
- It was observed that the concentration of polymers played a key role in evaluation studies.
- Films with permeation enhancer showed greater permeability than that of films without permeation enhancer.
- Formulation F4 and F10 were showed controlled release of drug for desired time of 24 h.

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Mr. Kambham Venkateswarlu: Has completed his masters in Pharmaceutical Sciences (Pharmaceutics) from Jawaharlal Nehru Technological University Anantapur, Ananthapuramu, Andhra Pradesh, INDIA and also completed more than 30 certifications from various international organizations like World Intellectual Property Rights Organization [WIPO], Switzerland and Alison, Ireland. He is also a recipient of Two Honorary Doctorates from LADC Institute, USA. Recently his biography was listed in Marquis Who's Who in the World as top 3% biographies in the country and also recipient of more than 10 National and International Awards. He has authored 5 International Books and more than 60 international scientific publications, amongst those, more than 15 were published in SCI indexed journals and also presented more than 10 scientific papers in various national and international conferences or seminars. He is also a one of the regular article writers for business magazines such as South Asia Ingredients magazine and member in several pharmacy associations like IPA etc. He is also acting as a Reviewer for the well known publishers such as Bentham Sciences, Science Domain International and some other ESCI Indexed journals such as Marmara Pharmaceutical Journal etc. He is involving in research since July-2012 [>4 Years] and these have been achieved within the span of 25 years of age.

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