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Formulation and evaluation of Nifedipine transdermal drug delivery system

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ABSTRACT

To prepare Matrix type transdermal patches of Nifedipine using different polymers in different ratios. 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 (USP 25., 2002). 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, an attempt was made to formulate an anti-hypertensive drug Nifedipine in the form of transdermal patches using different ratios of HPMC E15 and Eudragit L100. 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.

Keywords: Eudragit L100, Nifedipine, Transdermal drug delivery system, FTIR spectra, HPMC E15

INTRODUCTION [1-5]

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor bioavailability due to first pass metabolism and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be inconvenient [1].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 [5].

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 relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time [3]. 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 [2].

Anatomy of the skin [3-4]

The skin of an average adult human body covers a surface of approximately 2 m^2 and receives about one third of the blood circulating through the body. It is one of the most readily accessible organs of the human body with a thickness of only a few millimetres (2.97±0.28mm). Its major roles are to regulate body temperature, protect tissues from infection, prevent fluid loss, cushion internal structures. The skin can be divided into three distinct layers [3].

The epidermis is a multilayered structure consisting of cells in various stages of differentiation. The layer that interacts with the environment is the stratum corneum or horny layer. The stratum corneum consists of many layers of compact, flat, dehydrated and keratinized cells [3].

The dermis, approximately 2-3mm thick, forms the bulk of the skin and is made up primarily of fibroblasts. It consists of a network of collagen tissue fibers with interweaving blood and lymph vessels,

sweat and sebaceous glands, hair follicles and nerve endings (figure 1). The dermis consists of two regions, the papillary, or adventitial that interfaces the basal lamina, and the lower region, the reticular dermis [4].

The lowest layer of the skin is the hypodermis, which is primarily composed of fibroblasts and adipocytes. The hypodermis binds to the underlying structures, in addition to serving as a thermo-regulator and a cushion to internal organs against trauma [5].

Pathways of transdermal drug permeation [6-8]

There are critically three ways in which a drug molecule can cross the intact stratum corneum: via skin appendages (shunt routes); through the intercellular lipid domains; or by a transcellular route (figure 2). A particular drug is likely to permeate by a combination of these routes, with the relative contributions of these pathways to the gross flux governed by the physicochemical properties of the molecule [6].

Transcellular route [7]

Drugs entering the skin via the transcellular route pass through corneocytes. Corneocytes, containing highly hydrate keratin, provide an aqueous environment for which hydrophilic drugs can pass. The diffusion pathway for a drug via the transcellular route requires a number of partitioning and diffusion steps [7].

Intercellular route [6-7]

The intercellular pathway involves drug diffusing through the continuous lipid matrix. This route is a significant obstacle for two reasons. (i) Recalling the 'bricks and mortar' model of the stratum corneum, the interdigitating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which is in contrast to the relatively direct path of the transcellular route. (ii) The intercellular domain is a region of alternating structured bilayers. Consequently, a drug must sequentially partition into, and diffuse through repeated aqueous and lipid domains. This route is generally accepted as the most common path for small uncharged molecules penetrating the skin [6-7].

The appendgeal route [8]

Skin appendages provide a continuous channel directly across the stratum corneum barrier. However, their influence on drug penetration is hindered by a number of factors. The surface area occupied by hair follicles and sweat ducts are small (typically 0.1% of skins surface area), therefore limiting the area available for direct contact of the applied drug formulation [8].

Ideal characteristics of chemical penetration enhancers [8, 10, 12]

Ideally, penetration enhancers reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells. Some of the more desirable properties for penetration enhancer acting within the skin have been given as:

- It should be non-toxic, non-irritating and non-allergenic.
- It would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible.
- It should have no pharmacological activity within the body.
- The penetration enhancers should work unidirectionally, i.e., they should allow therapeutic agents into the body whilst preventing the loss of endogenous materials from the body.
- When removed from the skin, barrier properties should return both rapidly and fully to normal.
- It should be cosmetically acceptable with an appropriate skin feel.

Permeation enhancement techniques [9, 11]

The method employed for modifying the barrier properties of the stratum corneum to enhance drug penetration and absorption through skin may be classified into the following categories:

- 1. Chemical Enhancement Techniques
- 2. Physical Enhancement Techniques
- 3. Carriers/ Vehicles
- 4. Vesicular Carriers
- 5. Miscellaneous Techniques

Prodrugs and Ion-Pairs [12]

The prodrug approach has been investigated to enhance dermal and transdermal delivery of drugs with unfavourable partition coefficients. The prodrug design strategy generally involves addition of a pro-moiety to increase partition coefficient and solubility to increase the transport of the drug in the stratum corneum [11]. Upon reaching the viable epidermis, esterases release the active drug by hydrolysis thereby optimizing concentration in the epidermis. Charged drug molecules do not readily partition into or permeate through human skin. Formation of lipophilic ion pairs has been investigated to increase stratum corneum penetration of charged species. This strategy involves adding an oppositely charged species to the charged drug, forming an ion-pair in which the charges are neutralized so that the complex can partition into and permeate through the stratum corneum. The ion-pair then dissociates in the aqueous viable epidermis releasing the parent charged drug that can diffuse within the epidermal and dermal tissues [12].

MATERIALS AND METHODS

Materials: Nifedipine, a gifted sample from Aurabindo pharmaceuticals, HPMC E15, Eudragit L100 were purchased from Qualikem fine chemicals Ltd, Chloroform AR, Methanol AR were purchased from Merck Ltd, Mumbai. PEG, Calcium Chloride, Aluminium Chloride, Potassium dihydrogen Phosphate and Sodium hydroxide were purchased from Finar Chemicals Ltd, Ahmadabad.

Method:

Moisture Absorption Studies

The patches were weighed accurately and placed in the *desiccator* containing 100ml of saturated solution of Aluminium chloride, which maintains 84 % RH. After 3 days, the patches were taken out and weighed. The percentage moisture absorption was calculated using the following formula.

$$\%Moisture\ absorbtion = \frac{Final\ weight - \text{Initial weight}}{Initial\ weight} \times 100$$

Moisture Content Determination:

The patches were weighed accurately and placed in a desiccators containing calcium chloride at 40°C for 24 h. Then the final weight was noted when there was no further change in the weight of individual patch. The percentage of moisture loss was calculated as difference between initial and final weight with respect to final weight.

$$\%Moisture\ content = \frac{Initial\ weight - \text{Final weight}}{Initial\ weight} \times 100$$

***Ex vivo* permeation studies:**

Franz diffusion cell with a surface area of 4.15cm^2 was used for *ex vivo* permeation studies. The rat skin was mounted between the compartments of the diffusion cell with stratum corneum facing the donor compartment. The stratum corneum side of the skin was kept in intimate contact with their lease surface of the TDDS under test. A dialysis membrane was placed over the skin, so as to secure the patch tightly dislodged from the skin. The receiver phase was 24ml of phosphate buffer saline (PBS) pH7.4stirred at 500rpm on a magnetic stirrer .The amount of drug permeated was determined by removing 1 ml of sample at appropriate time intervals for 24h. The absorbance was measured at 338nm spectrophotometrically.Cumulative amounts of drug permeated in µg/cm^2 were calculated and plotted against time. Drug flux (µg/h/cm^2) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed skin surface.

***In vitro* release studies through Iontophoresis:**

Preparation of Ag/Agcl electrodes:

Pure silver wire with 0.5mm diameter was used as the anodal electrode and Agcl electrode was prepared by dipping Ag wire in silver chloride powder, this coated silver wire - Agcl electrode was used as cathodal electrode. These were connected to a power source.

Franz diffusion cells were used to perform transdermal iontophoretic *in vitro* studies. Rat abdominal skin was placed between the receptor and donor compartments of the diffusion cell and stirred at 500 rpm. The receptor compartment was filled with phosphate buffer 7.4 and tissue integrity test was conducted using methyl red solution in the donor compartment for about 3 hrs. After this skin was washed thoroughly and kept in place between the compartments then patch was placed above the skin. The anodal (Ag) electrode was placed in the donor compartment above the skin touching the patch and the cathodal electrode was inserted in the receptor compartment and a current of 0.5 ma/cm^2 is maintained for about 2 h then Iontophoresis was discontinued and passive diffusion was continued for 24 hours .The sampling method and time points were the same as in the *in vitro* release studies.

RESULTS AND DISCUSSION

Nifedipine is rapidly absorbed from the gastrointestinal tract and is subjected to an extensive first pass effect, giving an absolute bioavailability of about 12%.Nefidepine undergoes extensive metabolism in which less than 0.5% of the unchanged drug appears in the urine. Nifedipine is about 98% plasma protein bound, mostly to albumin shown in in vitrotestings. The plasma elimination half-life is approximately 10 h. In order to avoid the first pass metabolism of Nifedipine transdermal drug delivery is preferred. The aim of study is to prepare matrix type of Nifedipine Transdermal patch by using polymers HPMC E15 and Eudragit L 100 and to determine the drug release from these patches through iontophoresis.

The moisture content in the patches 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 is 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 content was found to increase with increasing the concentration of hydrophilic polymer (HPMC E15). The small moisture content in the formulations help them to remain stable and from being a completely dried and brittle film.

FTIR Compatibility Studies.

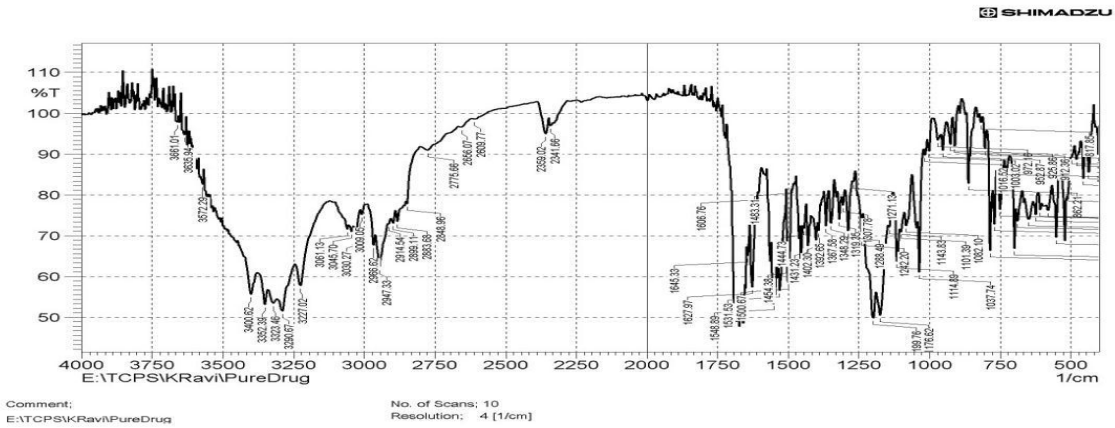

Figure 1: FTIR spectrum of drug and materials

Table 1: Drug content, % Moisture absorbed, %Moisture content of Nifedipine transdermal patches

Formulation	Drug content (mg)	%Moisture absorbed	%Moisture Content
F1	3.35±0.96	10.87±1.58	9.34±0.96
F2	2.83±1.29	7.92±1.82	4.62±0.85
F3	3.05±0.84	9.67±0.95	5.97±1.17
F4	3.26±1.18	8.39±1.46	8.35 ±1.32
F5	3.29±1.04	10.45±0.93	8.45±1.95
F6	2.73±0.55	6.42±1.25	4.58±0.77
F7	3.42±1.37	11.44±1.03	9.35±0.94
F8	2.99±0.92	8.35±0.89	5.21±0.55
F9	3.16±0.75	8.86±0.64	6.32±0.79
F10	3.32±1.55	9.34±0.59	7.56±0.82
F11	3.38±1.27	10.48±1.19	9.12±0.93
F12	2.76±0.86	6.54±1.53	5.89±1.87

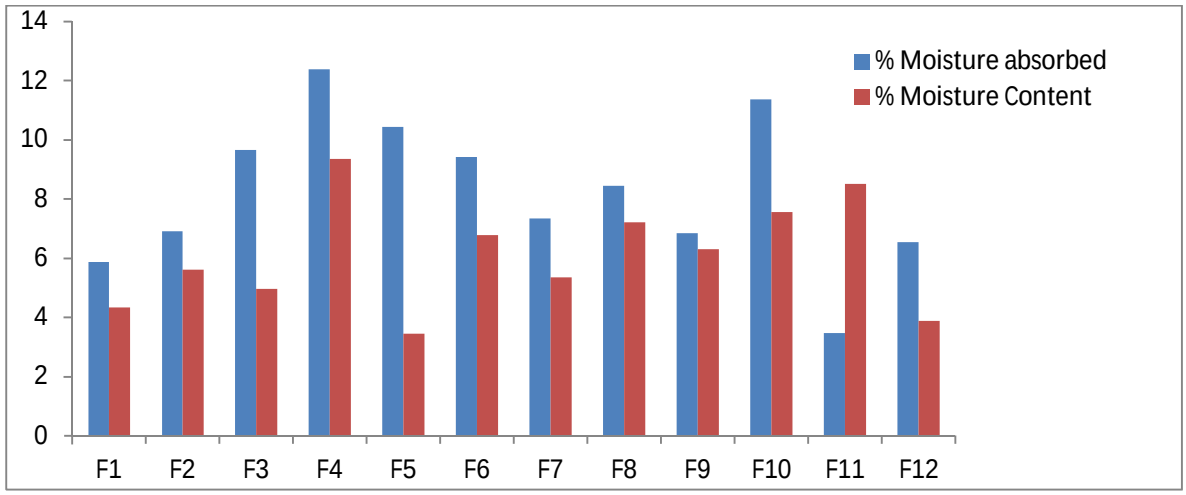

Figure 2: Moisture content of Nifedipine

Table 2: Permeation of Nifedipine from transdermal patches using iontophoresis (F1i to F6i)

Time (h)	Cumulative amount of drug permeated(µg/cm^2)		
	F1i	**F2i**	**F3i**
0	0	0	0
1	376.9±5.7	448.84±12.34	477.1±8.73
2	636.01±15.72	754.91±4.57	780.6±7.65
3	891.8±6.57	1033.83±10.33	1078.98±3.55
4	1190.18±9.35	1335.88±7.88	1373.68±9.79
5	1371.47±10.56	1520.48±9.75	1532.95±10.22
6	1584.33±8.79	1709.11±12.59	1798.3±5.55
7	1779.95±7.55	1910.96±10.73	1992.81±2.8
8	1949.5±12.33	2120.15±8.94	2241.26±13.45
9	2127.49±10.95	2285.3±7.45	2428.43±12.57
10	2253.38±9.22	2437.98±6.23	2592.12±4.95
12	2412.29±8.46	2627.72±6.59	2814.15±11.25
24	2756.17±14.52	3074.35±8.55	3246.84±8.82
Flux J_{ss}	35.14±1.42	38.57±0.54	40.73±0.94

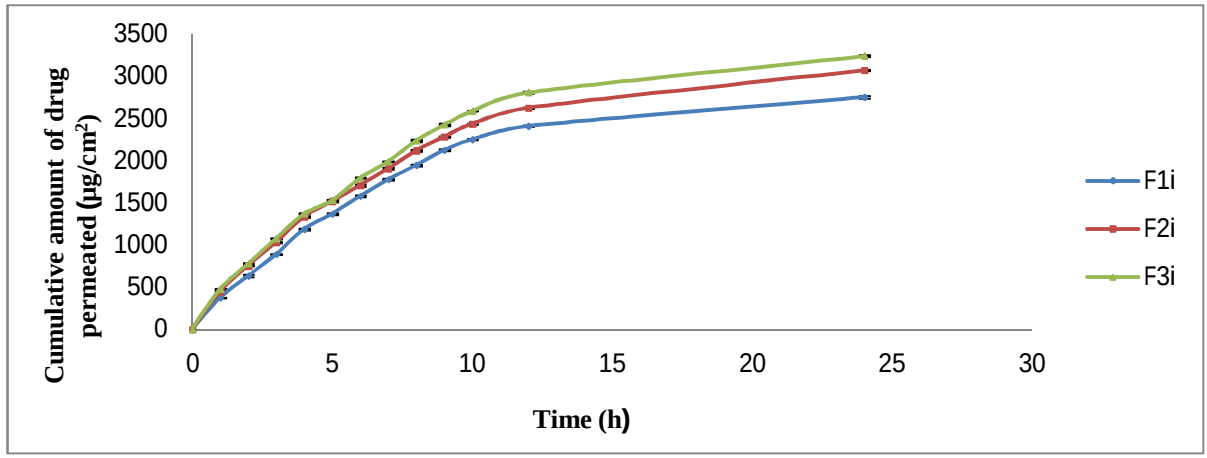

Figure 3: Permeation of Nifedipine from transdermal patches

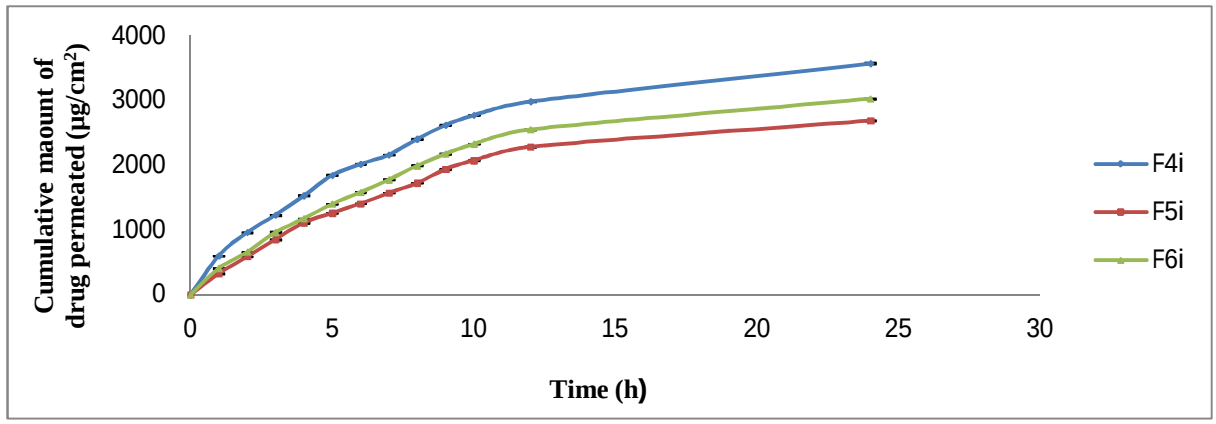

Figure 4: Permeation of Nifedipine from transdermal patches

Table 3: Permeation of Nifedipine from transdermal patches

Time (h)	Cumulative amount of drug permeated (µg/cm^2)		
	F4i	**F5i**	**F6i**
0	0	0	0
1	602.98±6.45	326.63±7.82	408.47±9.66
2	961.54±10.55	590.87±4.66	660.6±4.55
3	1228.34±14.52	852.54±9.55	962.64±13.45
4	1529.28±11.12	1110.9±8.94	1176.96±2.45
5	1844.9±7.29	1259.91±6.49	1400.8±5.89
6	2014.83±5.49	1405.61±5.33	1581.77±7.64
7	2160.52±9.58	1570.76±2.87	1775.17±8.92
8	2403.85±8.54	1723.79±6.22	1992.81±10.83
9	2617.81±8.22	1936.65±10.65	2175.2±12.47
10	2771.95±5.89	2070.98±9.76	2327.88±5.6
12	2982.6±12.38	2280.17±8.32	2550.65±11.41
24	3569.78±9.82	2686.44±7.52	3025.18±12.53
Flux J_{ss}	44.46±0.73	32.8 ±1.28	36.98±0.92

Table 4: Comparative study of Nifedipine permeation

Time (h)	Cumulative amount of drug permeated (µg/cm^2)		
	F4	**F10**	**F4i**
0	0	0	0
1	269.01±10.5	276.35±4.2	602.98±6.45
2	412.14±7.5	447.74±10.55	961.54±10.55
3	583.53±9.3	638.58±7.93	1228.34±14.52
4	751.24±8.9	822.08±2.95	1529.28±11.12
5	940.62±7.5	997.13±8.52	1844.9±7.29
6	1143.93±9.92	1221±3.78	2014.83±5.49
7	1351.66±9.35	1405.61±6.45	2160.52±9.58
8	1545.07±13.56	1585.4±12.56	2403.85±8.54
9	1773.71±14.5	1775.17±9.7	2617.81±8.22
10	2001.25±9.58	1987.14±10.69	2771.95±5.89
12	2252.27±12.12	2358.7±5.38	2982.6±12.38
24	3062.63±14.2	3227.78±6.74	3569.84±9.82
Flux J_{ss}	32.82±1.36	33.4±0.97	44.46±0.73

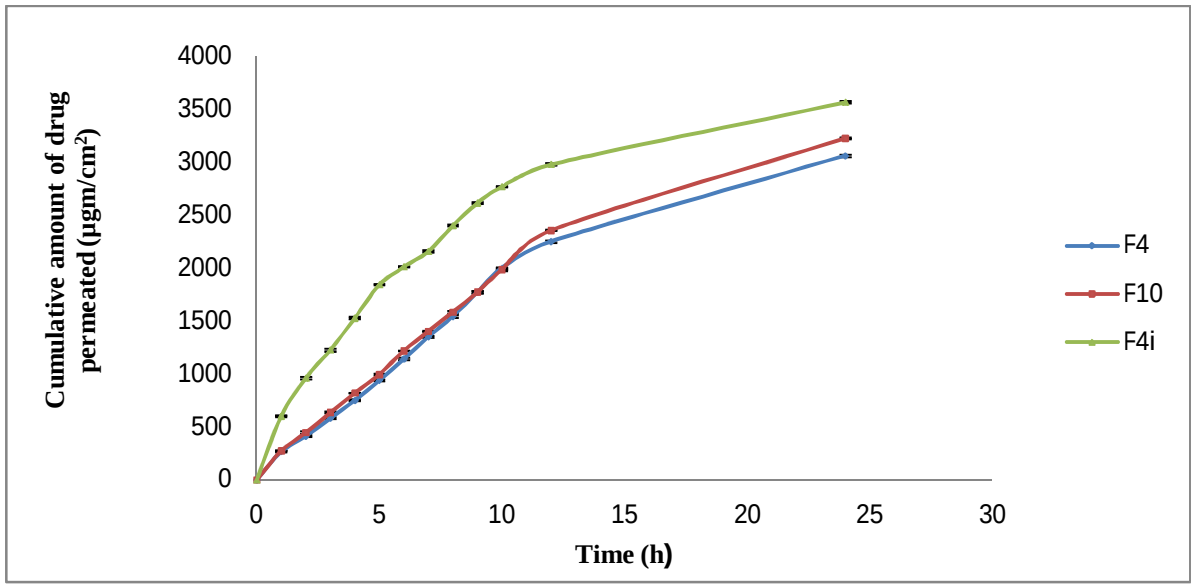

Figure 5: Comparative study of Nifedipine permeation

Ex vivo permeation studies gives the results of *in vitro* Nifedipine permeation through the rat skin from patches. The formulation F4 (HPMC E15 and Eudragit L100 ratio 10:2) exhibited the maximum (3062.63 µg) cumulative amount of drug permeation in 24 h, which was different from the formulation F1composed of HPMC E15 (2357.3µg). The formulation F10 (HPMC E15 and Eudragit L100, ratio 10:2) exhibited maximum (3227.78 µg) cumulative amount of drug permeation in 24 h, when DMSO was incorporated in the patch which was different from other formulations. The formulation F4i (HPMC E15 and Eudragit L100) i.e., through iontophoresis showed maximum (3569.78 µg) cumulative permeation and a flux of 44.46 µg/cm^2/h compared with formulations F4 and F10. Formulations F1 and F7 composed of HPMC E15 showed less drug permeation as rigid films were obtained.

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 E15 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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