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Formulation and Evaluation of Transdermal Patches of Nicorandil by Using Different Penetration Enhancer

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ABSTRACT

The purpose of this research was to develop a matrix-type transdermal patch containing drug Nicorandil with different ratios of Ethylcellulose 7 Cps and Eudragit Rs 100 polymeric systems by the solvent evaporation technique by using diethyl phthalate to the polymer weight, incorporated as a plasticizer. To enhance the permeation of drug through the skin by using different types of penetration enhancer like as DMSO, DMF, and Oleic acid are utilized. The prepared matrix patches were evaluated for their physicochemical characterization followed by weight variation, drug content estimation, folding endurance, moisture uptake, moisture loss, FTIR, and *in vitro* diffusion studies. The *in vitro* diffusion release study from different transdermal patches across the dialysis membrane. The polymer concentration of (Ethyl cellulose7 Cps: Eudragit RS 100) w/w in each type of as polymer Patch was found to be best. As the polymer concentration increase to be used 1:1 w/w, 2:1 w/w, 3:1w/w ratio. Ethyl cellulose in the concentration of 1% showed the best release as compared to other concentrations.

INTRODUCTION [1-7]

The novel drug delivery system thus point to releasing one or more drugs continuously for a fixed period of time in a predetermined pattern, either systemically to a specified target organ. When the objective of this study is to deliver the drugs through the skin in a predetermined manner, it is known as Transdermal Drug Delivery (TDD). Formulations on the skin can be classified into two categories according to the target site of action of the concerned drugs. One that has the systemic action after administration and the other exhibits localized effects in the skin.

Transdermal patch (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 advantages of a transdermal drug delivery route over other types of medication. The main objective of this study is to overcome degradation, gastric irritation and the first pass metabolism of the drug and to enhance skin permeability of drug by using suitable permeation enhancers. The patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. In the topical application of the drug, skin is commonly used as a site for administration of systemically active drugs, which involves the distribution of drug following absorption into the systemic circulation and then transported to the target site to achieve therapeutic action.

A self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin, at the controlled rate to the systemic circulation. Transdermal delivery provides leading edge over injectable & oral routes by increasing patient observance & avoiding the first-pass metabolism respectively.

1. MATERIALS & METHODS[8-10]:

1.1 MATERIAL

Nicorandil was received as a gift sample from Supriya Life Science Ltd., Mumbai. India. Ethyl Cellulose 7Cps, Eudragit RS 100 were purchased from Ozone International Mumbai, India. Diethyl phthalate was obtained from H.D. Lab Chm. Aurangabad respectively. All other

materials and chemicals used were of either pharmaceutical or analytical grade.

METHODS

General procedure for the preparation of transdermal patches:-

Transdermal patches containing Nicorandil were prepared by the solvent evaporation method. The polymers in selected ratios were weighed and dissolved in the specified solvent system. The plasticizer and enhancer were added to the polymeric solution and mixed uniformly for 20 min using a magnetic stirrer. Finally, the drug was incorporated with continuous agitation. The patches were prepared by the drug-loaded polymeric solutions in a Petri dish. The solution was evaporation at room temperature for a period of 24 hrs. The dried patches were packed in aluminum foil and stored in desiccators till further studies.

2. EXPERIMENTAL WORK:-

2.1 Experimental Methods

Preparation of phosphate buffer solution (pH 7.4):

Accurately measured 50 mL of 0.2 M potassium dihydrogen orthophosphate was transferred to a 200 ml volumetric flask and 39.1 ml of 0.2 M sodium hydroxide was added to it. Volume was made up to 200 ml with distilled water, mixed and pH was adjusted to 7.4.

2.2 Analytical methods:

Standard solution:

10 mg of Nicorandil was dissolved in 10 ml of pH 7.4 phosphate buffer to give a concentration of 1mg/ml (1000µg/ml).

Preparation of Nicorandil stock solution in pH 7.4 phosphate buffer:

From the above standard solution, 1 ml solution (1000 g/ml) is pipette out and diluted up to 10 ml which give 100µg/ml. From this solution 0.5 ml, 1 ml, 1.5 ml, 2 ml, 2.5 ml pipette out in a 10 ml volumetric flask and finally diluted up to the mark which gives required concentration that is

5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, and 25µg/ml**.**

3.3 Determination of Analytical Wavelength[11]

Calibration curve of Nicorandil in phosphate buffer (pH 7.4):

From the Nicorandil standard stock solution (100 µg/ml), appropriate aliquots were taken into different volumetric flasks and made up to 10 ml with phosphate buffer solution (pH7.4), so as to get drug concentrations of 5.0 to 25.0 µg/ml. The absorbencies of these drug Solutions were estimated at ʎmax 260 nm by using Shimadzu UV/visible 1800Spectrophotometer against phosphate buffer pH 7.4 as blank. This procedure was performed in triplicate to validate the calibration curve. The standard calibration curve yields a straight line, which indicates that the drug obeys Beers/ Lambert's range in the concentration range of 5- 25 µg/ml.

Table No.-1: Formulation of Nicorandil transdermal patches

Batch Code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Nicorandil (mg)	62	62	62	62	62	62
Ethyl cellulose 7Cps (mg)	250	335	375	250	335	375
Eudragit RS 100,(mg)	250	165	125	250	165	125
Dichloromethane (ml)	5	5	5	5	5	5
Methanol (ml)	5	5	5	5	5	5
Diethyl phthalate (ml)	1	1	1	1	1	1
DMSO				1		
DMF					1	
Oleic Acid						1
Dichloromethane (ml)	5	5	5	5	5	5
Methanol (ml)	5	5	5	5	5	5

3.4 Evaluation of Nicorandil transdermal patches[12- 17]:

➢ **Thickness**: The thickness of transdermal patches is determined by Vernier caliper, traveling microscope, dial gauge, screw gauge or micrometer at different points of the patch.

➢ **Weight uniformity:** The three randomly selected patches were used. For weight variation test, 3 patches from each batch were weighed individually and the average weight was calculated.

➢ **Drug content determination:** The patches at 2 cm^2 were cut and added to a beaker containing 100ml of Phosphate buffered solution of pH 7.4. The medium was stirred with a Teflon coated magnetic bead for 24 hrs. The solution was later filtered and analyzed for drug content with proper dilution at 260 nm spectrophotometrically.

➢ **Folding endurance:** The folding endurance was measured manually for the prepared patch. The patch (2 x2cm) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.

➢ **Percentage moisture absorption:** The percent moisture absorption test was carried out to check the physical stability and integrity of the patch in high humid conditions. In the present study, the moisture absorption capacities of the patch were determined in the following manner. The patch was weighed accurately and placed in the desiccators containing 100 ml of saturated solution of potassium chloride, which maintains 80-90% RH after 3 days, the films were taken out and weighed. The study was performed at room temperature. The percentage of moisture absorption was calculated using the formula.

$$\% \text{ Moisture uptake} = \frac{\text{Final Wt.} - \text{Initial Wt.}}{\text{Initial Wt.}} * 100$$

Percentage moisture loss: The prepared patch were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hours. After 24h, the patch reweighed and can determine the percentage of moisture loss from the below-mentioned

formula.

$$\% \text{ Moisture Loss} = \frac{\text{Initial Wt.} - \text{Final Wt.}}{\text{Final Wt.}} * 100$$

Surface pH: The patch was allowed to swell by keeping them in contact with 0.5ml of double distilled water for 1 hour in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1minute.

FTIR study

This mixture was then scanned over a wave number range of 4000 to 400 cm^{-1}. The FTIR of pure drug and physical mixture of formulation ingredients of the optimized batch were measured using Fourier Transform Infrared Spectrophotometer (Model FTIR8400S, Shimadzu, Japan). The amount of each formulation ingredient in the physical mixture was the same as that in the optimized batch. The pure drug and physical mixture were then separately mixed with IR grade.

3.5 FTIR spectroscopy:-

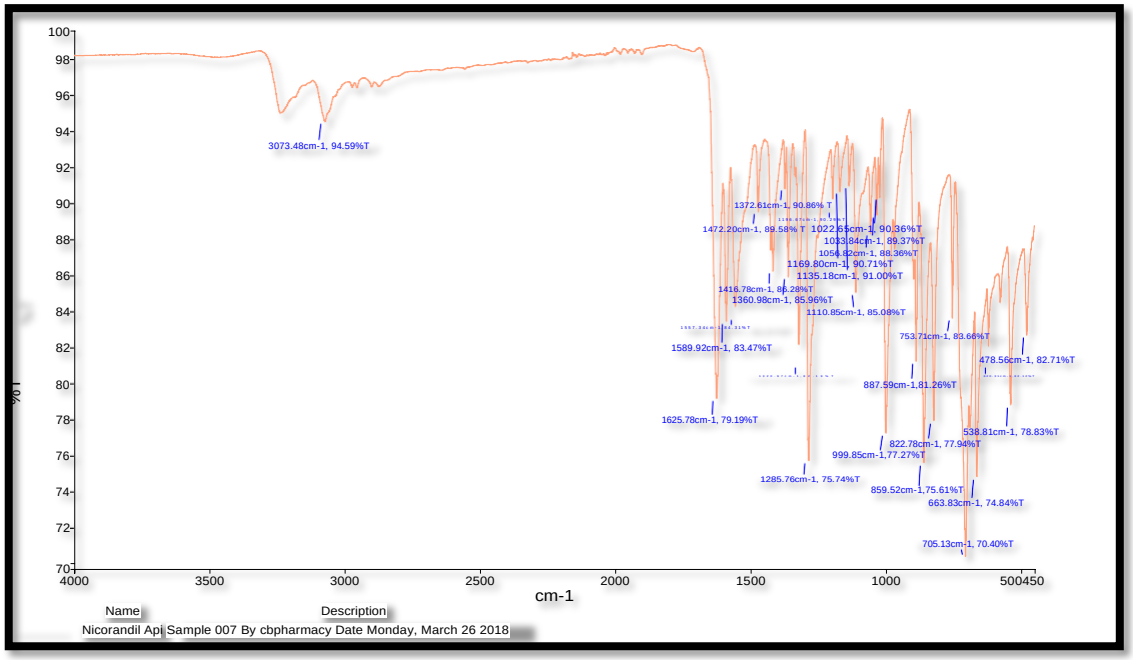

Figure No 1: FTIR spectra of Nicorandil

Table 2: Interpretation of FTIR Spectra of Nicorandil

Sr. No.	Functional Group	Standard peak (cm^{-1})	Peaks Observed(cm^{-1})
1	N-H stretching	3320-3370	3238
2	C=O stretching	1700-1750	1625
3	CO-NH	1550-1660	1589
4	O-NO2 stretching	1300-1220	1285
6	Aromatic pyridine tertiary amine	1310-1360	1360
7	C-O Stretching	1075-1020	1057

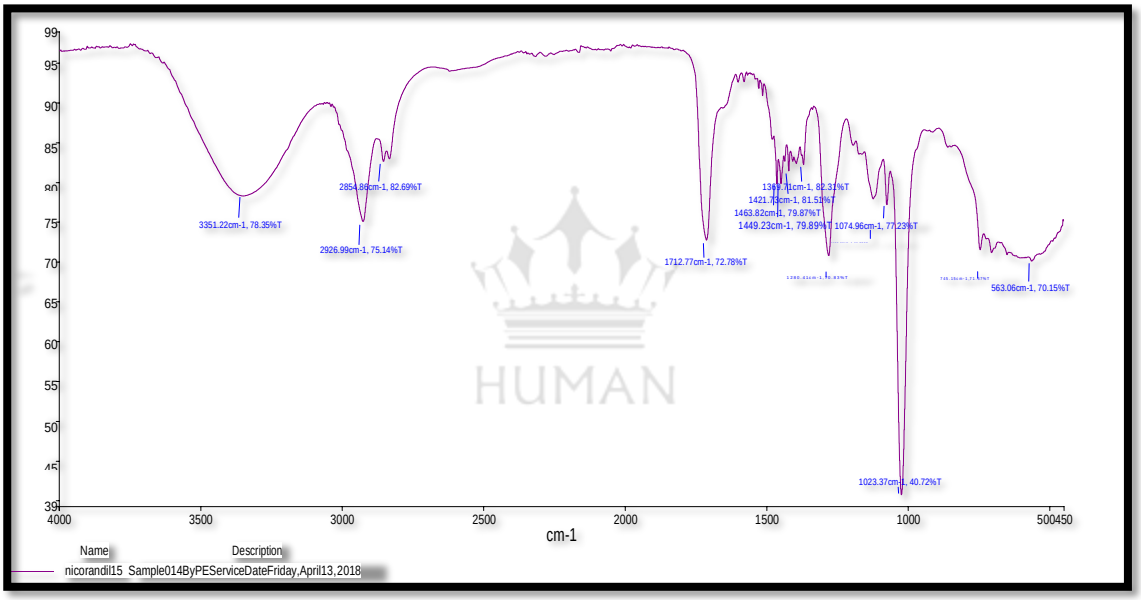

Figure No. 2: FTIR spectra of Nicorandil +Ethyl cellulose +Eudragit RS100

3.5.1 Evaluation of Nicorandildrugs

3.5.2 *In vitro* diffusion studies:

The present work, an attempt has been made to increase the % drug release of Nicorandil with changes in the concentration of polymers & plasticizers by a solvent evaporation method.

Table No-3: *In vitro* diffusion study of Nicorandil [F1-F3]

Time (hr.)	% drug release		
	F1	F2	F3
1	8.36	7.4	8.36
2	14.34	15.4	12.3
3	22.89	23.15	21.17
4	29.15	30.22	28.2
5	36.89	37.12	35.89
6	43.22	44.81	42.2
7	50.11	52.17	49.73
8	59.8	60.3	62.45

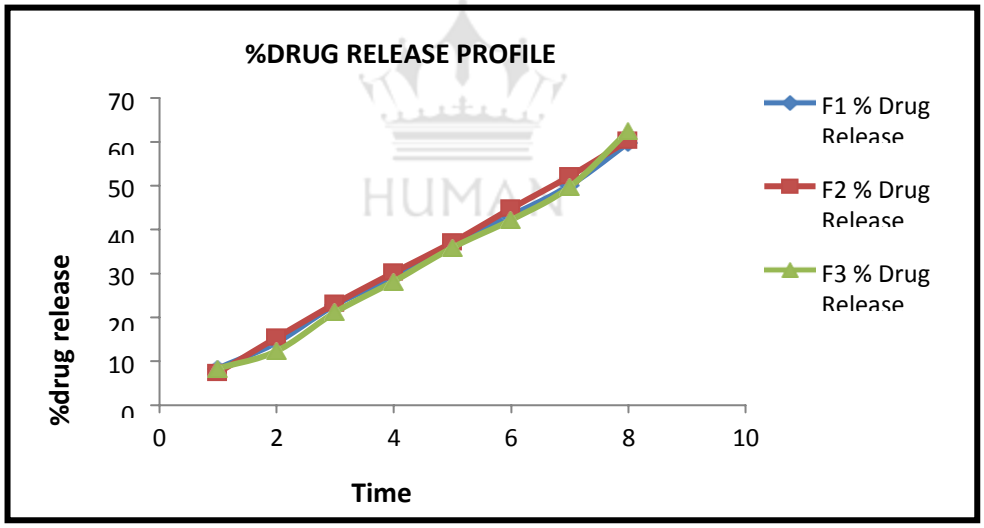

Figure No. 3: *In vitro* diffusion study Nicorandil of batches F1-F3

Table No.4: *In vitro* dissolution study of Nicorandil [F4-F6]

Time (hr.)	% drug release		
	F4	F5	F6
1	7.40	6.40	9.12
2	18.05	19.10	17.12
3	28.36	29.20	26.20
4	39.86	40.12	38.15
5	51.42	52.32	53.17
6	63.50	62.51	61.50
7	74.70	73.12	74.30
8	82.18	87.10	91.10

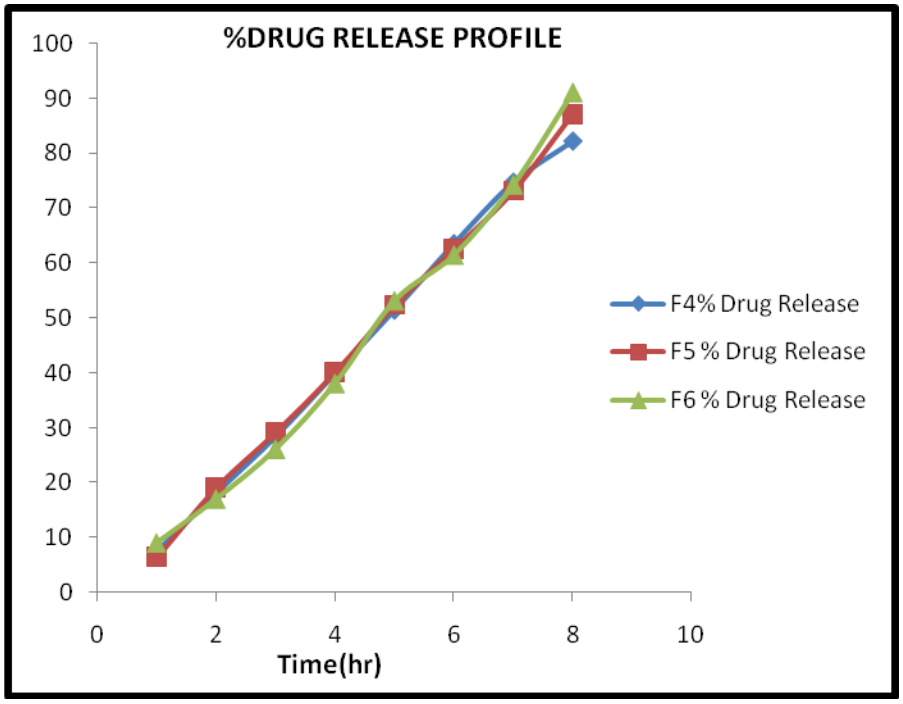

Figure No. 4: In- vitro diffusion study Nicorandil of batches F4-F6

Table No.-5: Permeability coefficients, the flux of Nicorandil with different enhancers

SR. NO.	ENHANCER	PERMEABILITY COEFFICIENT (cm/hr)	FLUX (µg/cm2/hr)
1	Pure drug	50.20	75.63
2	Oleic Acid	94.78	94.78
3	DMSO	72.95	72.95
4	DMF	80.18	80.18

Table No.6: Evaluation parameter of Transdermal patch

Batch code	Weight uniformity (g/cm2)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture Content uptake	Moisture Content loss
F1	0.156±0.0055	0.28±0.0020	91±1	91.46%	1.29±0.32	1.80±0.72
F2	0.190±0.0015	0.38±0.0017	104±5.24	93.90%	1.49±0.25	1.61±0.29
F3	0.094±0.0036	0.19±0.0021	97±6.42	92.68%	2.06±0.18	1.12±0.35
F4	0.148±0.0080	0.29±0.0033	122±8.32	97.56%	1.22±0.69	3.33±0.25
F5	0.108±0.006	0.24±0.0066	89±3.51	98.78%	1.86±0.91	2±0.12
F6	0.127±0.002	0.25±0.0031	72±6.02	97.56%	1.36±0.54	1.62±0.60

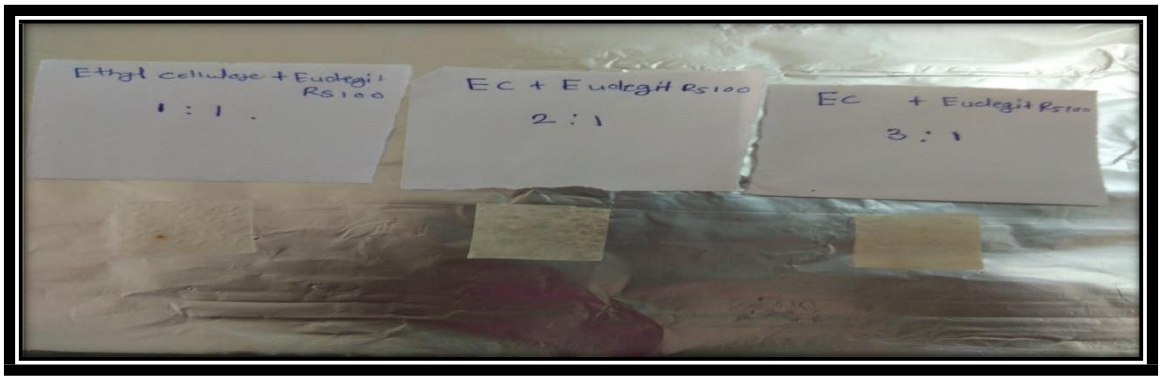

Figure No.-5: 2X2 cm Formulation of a transdermal patch

5.1 Stability study

The stability study conducts by ICH (International Conference on Harmonization) guideline. It showed No significance change in properties of the optimized formulation & the drug release. Short term stability studies were performed in a Stability chamber over a period of 1 month on the promising transdermal patch formulation F6. A sufficient number of patch formulation were packed in a container and kept in a Stability chamber at Temperature 45^0C & RH 75%. Samples were taken on 1 month for drug content estimation; also the thickness, weight, folding endurance and in-vitro dissolution studies were performed to determine the drug release profile.

Table No.-7: accelerated stability study

Batch Code	Weight uniformity (g/cm2)	Thickness (mm)	Folding endurance	Drug Content (%)	Moisture Content uptake	Moisture Content loss	% drug release
F6 before stability	0.127±0.002	0.25±0.0031	72±6.02	97.56%	1.36±0.54	1.62±0.60	91.10
F6 After Stability	0.125±0.002	0.25±0.0031	72±6.02	96.26%	1.36±0.54	1.62±0.60	89.75

DISCUSSION

Development of a transdermal patch is a suitable method to increase bioavailability. A different formulation of a transdermal patch in evaluation parameters results were observed, F6 formulation was found to be the best formulation. The transdermal patch formulation of FTIR studies concluded that was no interaction between drug and excipients. (EC 7cps, Eudragit Rs 100, DMSO, DMF, Oleic acid and diethyl Phthalate).

F1 which is containing Ethylcellulose 7 Cps: Eudragit RS 100 (1:1) showed drug release for 8 hrs. Formulation F2 containing EC 7cps: Eudragit RS 100 (2:1) shows comparable release. The formulation F3 containing EC 7cps: Eudragit RS 100 (3:1) shows release. The patches F4 to F6 were prepared by incorporating permeation enhancers, which showed the promising result.

For F1, F2, F3 formulations were found at 59.80%, 60.30%, 62.45% of Nicorandil was released. Even though the sustained effect was achieved to a greater extent complete drug release. So it necessitates further study to release the complete drug from the prepared formulations. The permeation enhancers choose for the studies were oleic acid, DMSO, and DMF in formulations F4 to F6 respectively.

In the formulation F6, oleic acid was used as a permeation enhancer and the drug release response was studied. The drug release from this patch was found to be 91.10%. The result of oleic acid significantly increased the release, when compared to the formulation without enhancer i.e. F1 to F3.

DMSO was tried in the formulation F4 drug release shows 82.18%at 8 hrs. DMF was tried in the formulation in F5 drug release shows 87.10%. Oleic acid was tried in the formulation F6 drug release shows 91.10%. The patch containing oleic acid as an enhancer shows the maximum release of 8 hrs and emerges as the best formulation F6.

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