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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF NICORANDIL

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ABSTRACT

Transdermal patch has made an important contribution to medical practice. It is a medicated patch that delivers a specific amount of medication through the skin into the blood stream. An advantage of a transdermal patch route over other types of medication delivery is that 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. The present investigation was aimed to formulate transdermal patches of Nicorandil drug with different ratios of Ethyl cellulose7Cps and Eudragit Rs 100 polymeric systems by the solvent evaporation technique by using Diethyl phthalate to the polymer weight, incorporated as plasticizer. To enhance the permeation of drug through the skin by using different types of penetration enhancer like as DMSO, DMF, and Oleic acid. The prepared matrix patches were evaluated for their physicochemical characterization followed by weight variation, drug content estimation, folding endurance, moisture uptake, moisture loss, FTIR, skin irritation and in vitro diffusion studies. The in vitro diffusion release study from different transdermal patches across the dialysis membrane. 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 concentration of 1% showed best release as compared to other concentrations.

KEYWORDS: Transdermal patches, Nicorandil, Ethyl cellulose 7-cps, Eudragit RS 100, Penetration Enhancer.

INTRODUCTION[1,2,3,4,5,6,7]

Transdermal patch generally refers to topical application delivers agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. The application of transdermal delivery to a wider range of drugs is limited due to the significant barrier to penetration across the skin which is allied primarily with the outermost stratum corneum layer of the epidermis. When the objective of this study is to deliver the drugs through skin in predetermined manner, it is known as Transdermal Drug Delivery (TDD). Formulations on 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 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 topical application of drug, skin is commonly used as a site for administration of systemically active drugs, which involves 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 controlled rate to the systemic circulation. Transdermal delivery provides leading edge over inject able & oral routes by increasing patient observance & avoiding first pass metabolism respectively.

MATERIALS AND METHODS[8,9,10,11]

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 specified solvent system. The plasticizer and enhancer were added to the polymeric solution and mixed uniformly for 20 min using magnetic stirrer. Finally the drug was incorporated with continuous agitation. The patches were prepared by the drug loaded polymeric solutions in a petridish. 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.

Table No. 1: Formulation of Nicorandil transdermal patches.

Batch Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nicorandil (mg)	62	62	62	62	62	62	62	62	62
Ethyl cellulose 7Cps (mg)	250	335	375	250	335	250	335	250	335
Eudragit RS 100, (mg)	250	165	125	250	165	250	165	250	165
Dichloromethane (ml)	5	5	5	5	5	5	5	5	5
Methanol (ml)	5	5	5	5	5	5	5	5	5
Diethyl phthalate (ml)	1	1	1	1	1	1	1	1	1
DMSO				1	1				
DMF						1	1		
Oleic Acid								1	1
Dichloromethane (ml)	5	5	5	5	5	5	5	5	5
Methanol (ml)	5	5	5	5	5	5	5	5	5

Evaluation of Nicorandil transdermal patches[12,13,14,15,16,17]

- **Thickness**: The thickness of each patch was measured by using Vernier caliper, screw gauge at five different positions of the patch and the average was calculated.
- **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 100 ml 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 at high humid conditions. In the present study the moisture absorption capacities of the patch were determined in the following manner. The patch were 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 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 desiccators containing fused calcium chloride at room temperature for 24 hours. After 24h, the patch reweighed and can determine the percentage 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 optimized batch were measured using Fourier Transform Infrared Spectrophotometer (Model FTIR8400S, Shimadzu, Japan). The amount of each formulation ingredient in the physical mixture was same as that in the

optimized batch. The pure drug and physical mixture were then separately mixed with IR grade.

FTIR spectroscopy

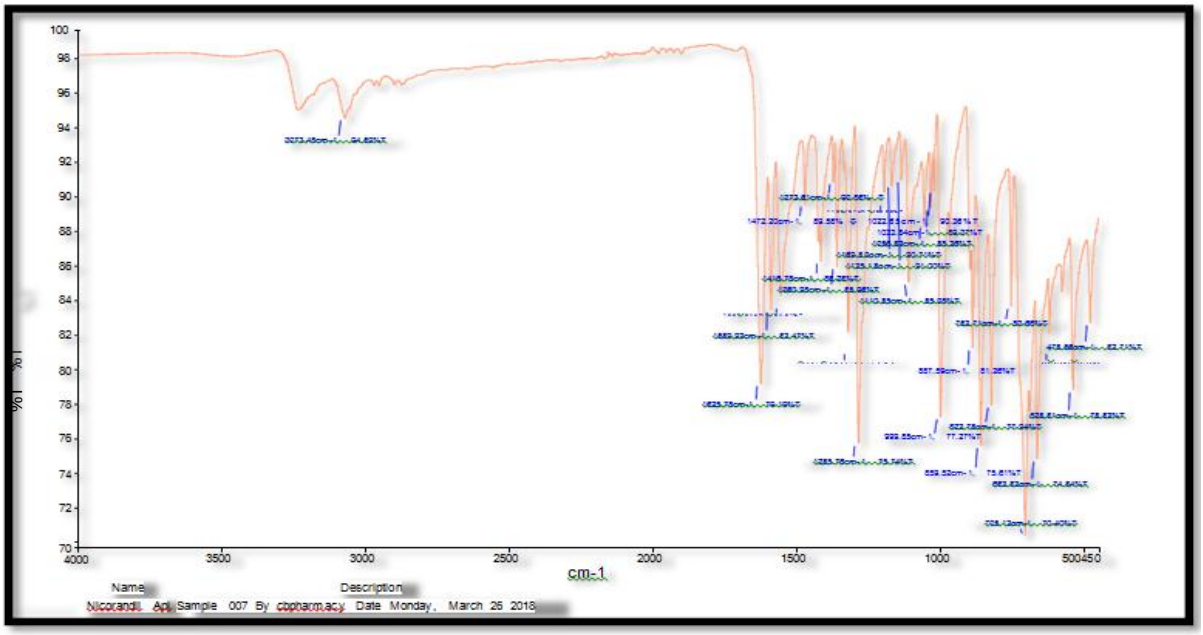

Figure No 1: FTIR spectra of Nicorandil.

Table 2: Interpretation of FTIR Spectra of Nicorandil.

Sr. No.	Functional Group	Standard peak	Peaks Observed
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

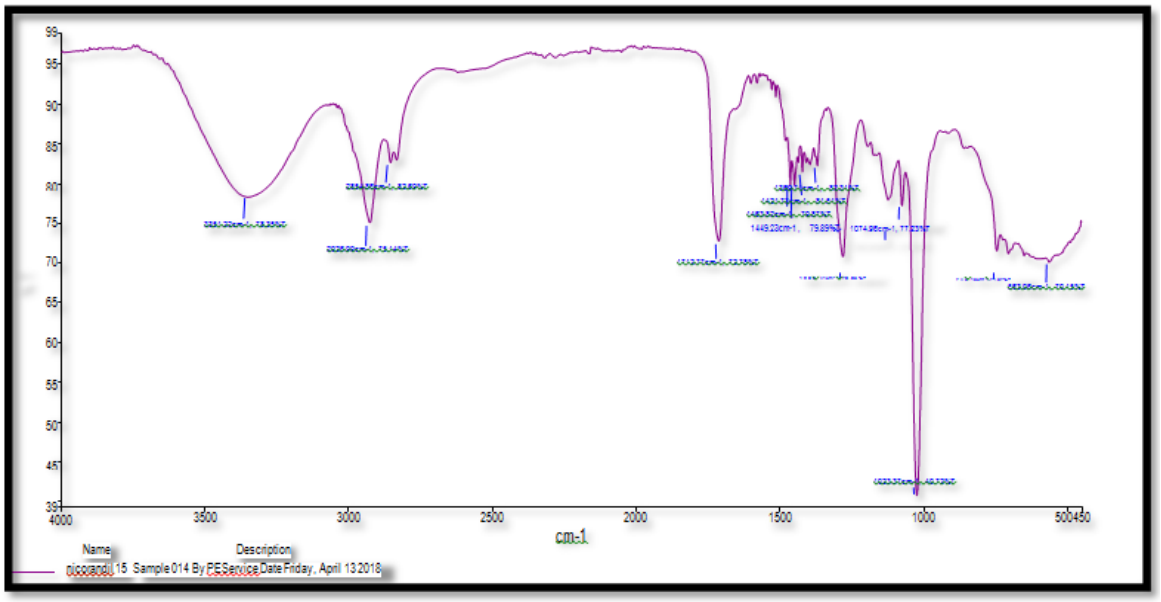

Figure No. 2: FTIR spectra of Nicorandil +Ethyl cellulose +Eudragit RS100.

Evaluation of Nicorandil drugs

In-vitro diffusion studies

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

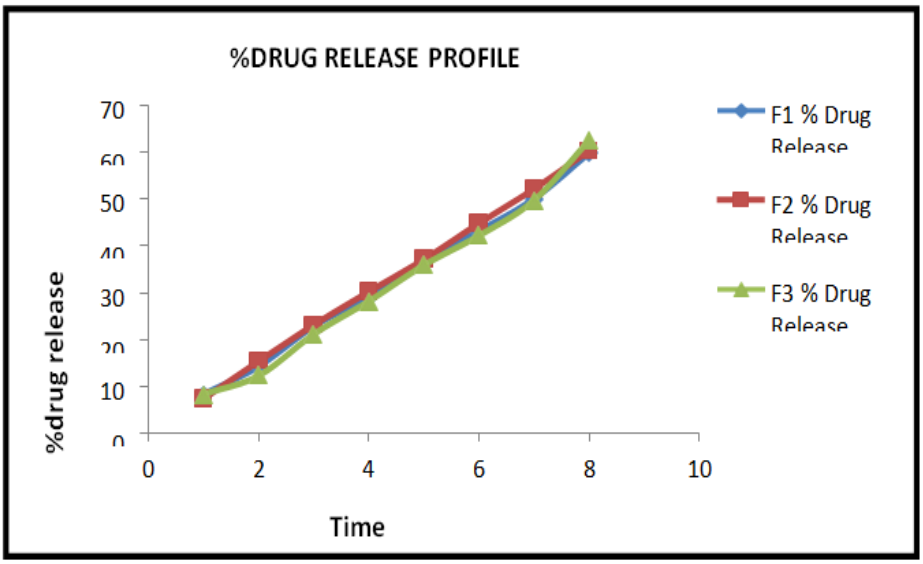

Figure No. 3: In- vitro diffusion study Nicorandil of batches F1-F3.

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

Tim (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

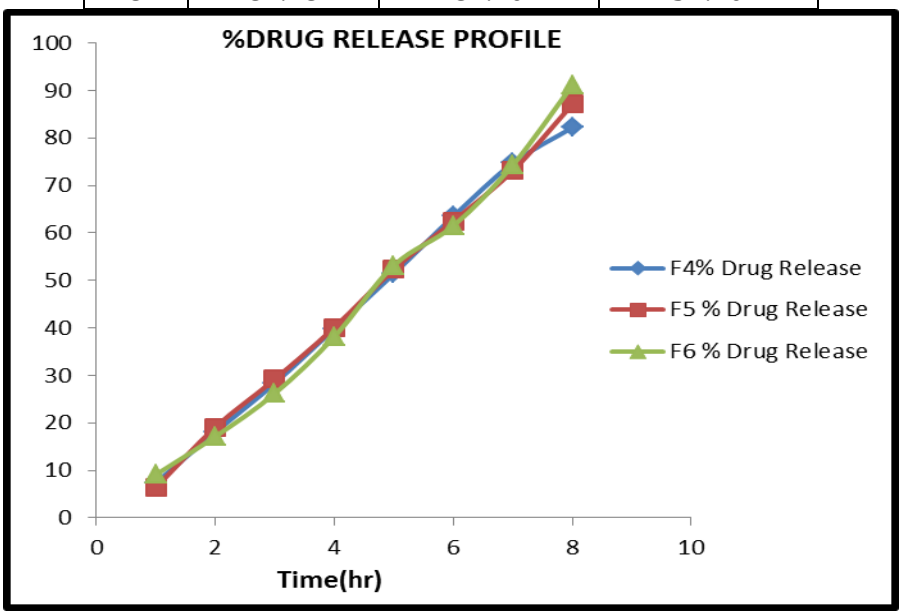

Figure No. 4: In- vitro diffusion study Nicorandil of batches F4-F6.

Table No. 5: In-vitro dissolution study of Nicorandil [F7-F9].

Time (hr.)	% drug release		
	F7	F8	F9
1	10.51	9.65	8.36
2	17.10	17.86	20.09
3	26.89	30.12	32.45
4	39.40	41.68	45.47
5	46.15	53.04	58.36
6	60.12	63.12	69.14
7	82.40	74.17	82.15
8	89.12	90.18	94.89

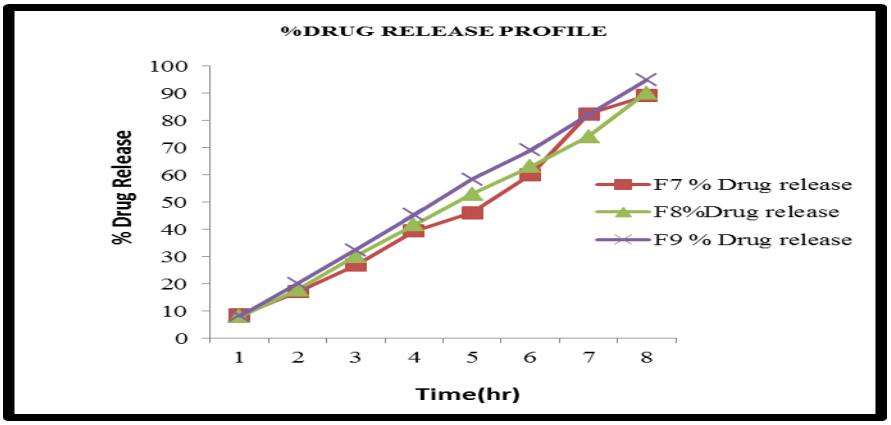

Figure No. 5: In- vitro diffusion Nicorandil of batches F7-F9.

Table No. 6: Permeability coefficients, 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. 7: 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
F7	0.118±0.0025	0.23±0.0015	97±6.02	98.78%	2.4±0.12	1.93±0.54
F8	0.112±0.0062	0.26±0.0057	82±6	98.78%	1.70±0.94	2.63±0.15
F9	0.144±0.0081	0.22±0.0015	97±4.16	98.78%	1.48±0.14	1.50±0.37

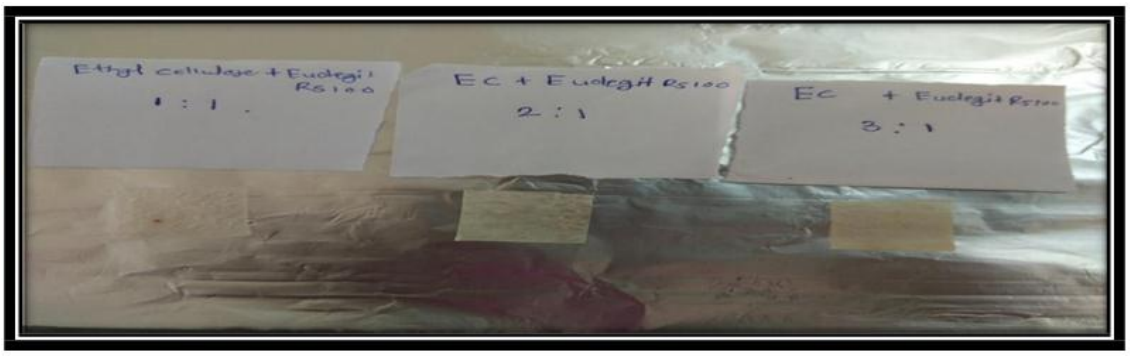

Figure No. 5: 2X2 cm Formulation of transdermal patch.

Skin Irritation Studies

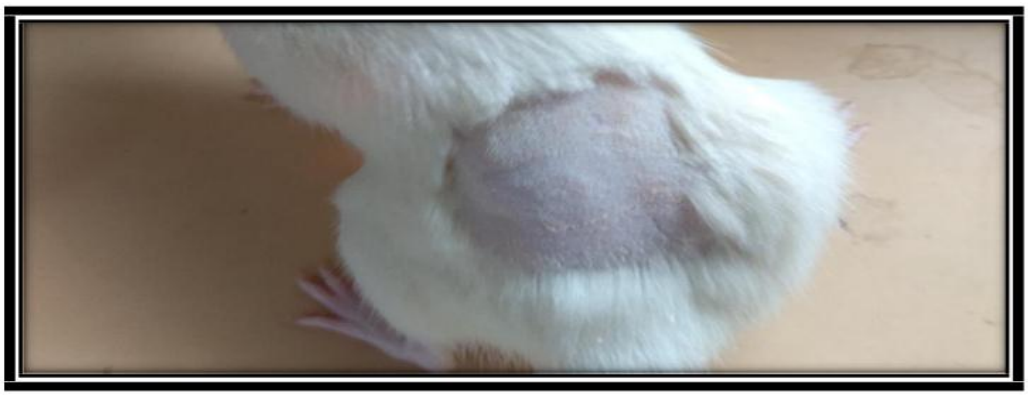

Figure No. 6: Rat skin after shaving.

Figure No. 7: Rat skin after application of patch.

Figure No. 8: Rat skin after removing patch.

There is no Erythma or Edema Found on Rat Skin.

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 F9. Sufficient number of patch formulation were packed in 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. 8: Accelerated stability study.

Batch Code	Weight uniformity (g/cm2)	Thickness (mm)	Folding endurance	Drug Content (%)	Moistur e Content uptake	Moisture Content loss	% drug release
F9 before stability	0.144±0.0081	0.22±0.0015	97±4.16	98.78%	1.48±0.14	1.50±0.37	94.89
F9 After Stability	0.143±0.0081	0.22±0.0015	97±4.16	97.38%	1.48±0.14	1.50±0.37	92.19

DISCUSSION

Development of transdermal patch is a suitable method to increase bioavailability. Different formulation of transdermal patch in evaluation parameters results were observed, F9 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 Ethyl cellulose 7 Cps: Eudragit RS 100 (1:1) showed drug release 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 F9 were prepared by incorporating permeation enhancers, which showed promising result.

For F1, F2, F3 formulations were found 59.80%, 60.30%, 62.45% of Nicorandil was released. Even though 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 F9 respectively.

In the formulation F9, 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 94.89%. The result 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, F5 drug release shows 82.18%, 87.10% at 8 hrs. DMF was tried in the formulation in F6, F7 drug release shows 91.10%, 89.12%. Oleic acid was tried in the formulation F8, F9 drug release shows 90.18%, 94.89%. The patch containing oleic acid as an enhancer shows maximum release of 8 hrs and emerges as a best formulation F9.

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