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ORIGINAL ARTICLE

Design and Evaluation of Transdermal Patches of Nicorandil

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ABSTRACT

Objectives: The purpose of this study was to develop a transdermal patch containing the drug nicorandil with different ratios of Eudragit RL 100 polymeric by solvent casting method.
Methods: The prepared patches were evaluated for physicochemical characterization, thickness uniformity, mass uniformity, drug content uniformity, folding endurance, moisture loss, FTIR, SEM, in vitro release, ex vivo permeation, and stability studies.
Findings: The results of the studies suggest that formulated transdermal patches with good physical properties and drug content were obtained by the solvent casting method. Surface morphological studies indicated uniform distribution of drugs in the polymeric patch formulation. The in vitro diffusion study suggested that drug release was controlled by all six formulations in comparison with the pure drug. The cumulative release of the drug in phosphate buffer pH 6.8 from formulations (F1-F6) ranged between 89.55±0.62- 78.52±0.63% in a 12-hour study. Ex vivo results showed a good correlation with the in vitro study results. About 89.55±0.62% of the drug from (F4=drug: polymer 1:4) permeated through the rat abdominal skin sample over a period of 12 h.
Novelty: Transdermal patches could be a good alternative for controlled drug therapy with nicorandil.

Keywords: Nicorandil; Eudragit; Transdermal patches; Controlled release; In vitro release

INTRODUCTION

The conventional dosage forms, including tablets, capsules, ointments, liquids, and injectable drugs, have been primary means for treating both acute diseases and chronic illnesses, by administering drugs to patients. This type of drug delivery system promotes drug release. To ensure that the drug concentration remains within the therapeutic range required for effective treatment, it is necessary to administer this type of drug delivery system multiple times per day. This results in significant fluctuations in drug levels. Further, the conventional dosage forms used for the control of infection, pain and fertility may cause side effects like nausea, vomiting, gastric irritation, and toxicity if they are consumed for long duration [1].

Thus, the novel drug delivery system points to releasing one or more drugs continuously for a fixed period of time in a predetermined pattern, either systemically or to a specified target organ. Transdermal drug delivery systems (TDDS) are also known as "patches" [2]. Transdermal therapeutic systems are a type of self-contained, discrete dosage form that delivers a drug at a controlled rate to the systemic circulation when applied to intact skin. The ability of TDDS to deliver drugs with systemic effects through intact skin while bypassing first-pass metabolism has accelerated transdermal drug delivery research in the field of pharmaceutics. Skin formulations can be classified into two categories according to the target site of action of the drugs. One has systemic action after administration, and the other exhibits localized effects in the skin [3,4]. Transdermal systems are typically designed to administer actives at a constant rate for several hours to days after application to the skin in a manner that approximates zero-order kinetics [5]. The advantage of using a transdermal drug delivery route over other types of medication is that it allows for the controlled release of the medication into the patient. This is typically achieved through a porous membrane that covers a reservoir of medication or by melting thin layers of medication embedded in the adhesive. The application of drugs to specific areas of the body is a common method

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for administering systemically active drugs. These drugs are absorbed into the systemic circulation and transported to their target site to produce a therapeutic effect. This route of administration is often used for drugs that need to be applied directly to a particular area of the body. A self-contained, discrete dosage form which, when applied to intact skin, delivers the drug through the skin at a controlled rate to the systemic circulation. Transdermal delivery offers an advantage over injectable and oral routes because it enhances patient compliance and bypasses the first-pass metabolism.

Nicorandil (N-[2-hydroxyethyl] nicotinamide nitrate [ester]) is one of the most emerging molecules belonging to a class of compounds known as potassium channel activators. It is the first therapeutic molecule to hyperpolarize muscle cell membranes and is a potent coronary vasodilator, which exerts its action by arteriodilation and vasodilation. It has an oral bioavailability of approximately 75%, protein binding around 25%, a short half-life of about 1 h, and the usual oral dosage regimen is 5–40 mg taken two-four times a day. The undesirable consequences of nicorandil use may include headaches, and dilation of blood vessels, resulting in flushing, nausea, vomiting, and loss of strength. Oral ulceration has long been recognized as a major side effect of nicorandil treatment, but more recently, it has been associated with ulceration of any region of the gastrointestinal tract, including the perianal area, and may cause withdrawal of nicorandil[6]. To promote better patient compliance and decrease the need for regular administration, it would be beneficial to prescribe nicorandil as a TDDS at a single daily dose. Hence, this study involved the development and evaluation of transdermal drug delivery systems containing nicorandil[7–10].

METHODS

The reagents used in this study were of pharma grade or the best possible laboratory reagent (LR) supplied by the manufacturer, and double-distilled water was used in all experiments.

Preformulation studies

Preformulation testing was performed to investigate the physiochemical properties of the drug substance alone and in combination with excipients.

Melting point determination

Melting point determination of the obtained drug samples was performed using the open capillary method. The drug was taken in a glass capillary whose end was sealed by a flame. The capillary-containing drug was dipped in liquid paraffin inside a melting point apparatus. The melting point is a good first indication of the purity of the sample because the presence of a relatively small amount of impurity can be detected by lowering and widening the melting point range.

Determination of lambda max

A stock solution of 1 mg/ml nicorandil was prepared by dissolving 100 mg of the drug in 100 ml phosphate buffer solution (PBS) at pH 6.8. The stock solution was then diluted to a concentration of 10 μg/ ml. The solution was scanned between 200 nm and 400 nm.

Calibration curve of Nicorandil in phosphate buffer pH 6 8

A stock solution of 1 mg/ml nicorandil was prepared by dissolving 100 mg of the drug in 100 ml phosphate buffer solution (PBS) at pH 6 .8. The stock solution was diluted to obtain Beer's concentration range of 5 to 40 mcg/ml. A calibration curve was constructed by plotting the absorbance vs. concentration.

Formulation of nicorandil loaded patches[11]

A transdermal patch of nicorandil was prepared using the solvent casting method for the formulations shown in Table 1. The weighed quantity of Eudragit was dissolved in 25 ml acetone. To the above solution, the required quantity of nicorandil was added and 0.1 ml of plasticizer was mixed and stirred for 10 min. The drug-polymer solution was cast in a Petri dish and dried at room temperature for 24 hours. An inverted funnel was placed over the Petri dish to prevent air currents. After drying, the patches were peeled from the Petri dish, wrapped in aluminum foil, and preserved in desiccators for further studies.

Table 1: Formulation

Ingredients	F1	F2	F3	F4	F5	F6
Nicorandil (mg)	450	450	450	450	450	450
Eudragit RL-100 (mg)	500	1000	1500	2000	2500	3000
Glycerin (mL)	0.5	0.5	0.5	0.5	0.5	0.5
Acetone (mL)	25	25	25	25	25	25

Characterization of patches[12,13]

Physical appearance

The prepared patches were examined for colour, clarity, and surface texture.

Thickness uniformity[14]

The thickness of the patches was measured using a Vernier caliper with a minimum count of 0.01 mm. The thickness was measured at three different points on the film, and the average readings were taken.

Mass uniformity[15]

A patch of size 2×2 cm^2 was cut, the weight of each patch was taken individually, and the average weight of the patch was calculated.

Folding endurance

The folding endurance was measured manually for the prepared patches. A strip of the patch (2×2 cm^2) was cut and repeatedly folded at the same place until it broke. The number of times the film could be folded at the same time without breaking gave the value of the folding endurance.

Percentage moisture loss

The patches were individually weighed and stored in a desiccator containing calcium chloride. The final weight was noted, and there was no change in the weight of the individual patches. The percentage moisture content was calculated as the difference between the initial and final weights with respect to the final weight.

Drug content uniformity[16]

The patches were then tested for content uniformity. Patches of size 1 cm^2 were cut and placed in a 100 ml volumetric flask. The contents were stirred using magnetic beads for 24 hours to dissolve the patches. Subsequent dilutions were prepared using a phosphate buffer (pH 6.8). The absorbance of the solution was measured against the corresponding blank solution at 260 nm by using a UV-visible spectrophotometer. The experiment was repeated three times to validate the results.

Drug polymer interaction by Fourier Transform Infrared (FTIR) Spectroscopy

Infrared spectra of the pure drug, physical mixture of drug with polymers, and formulation were obtained using the KBr pellet technique and were recorded in the range of 4000 – 400 cm using an FTIR Spectrophotometer.

Scanning electron microscopic analysis of Nicorandil patches

The patches were mounted onto stubs using double-sided adhesive tape and sputter-coated with platinum using a sputter-coater. The patches were observed under the SEM at the required magnification at room temperature. The acceleration voltage used was 10 kV, and the secondary electron image was used as a detector.

In vitro release studies[17–19]

The fabricated patches were cut into 2.5 cm^2 and placed on the commercial semi-permeable membrane (regenerated cellulose which was permeable to low molecular weight substances) and attached to the diffusion cell such that the cell's drug-releasing surface towards the receptor compartment which was filled with phosphate buffer solution of pH 6.8 at 37 $\pm$ 1°C. The elution medium was then magnetically stirred. Aliquots (1 mL) were withdrawn at predetermined time intervals and replaced with equal volumes of phosphate buffer (pH 6.8). The drug content of the samples was analyzed using a UV spectrophotometer at 262 nm.

Ex vivo permeation studies

An ex vivo permeation study was performed on albino rats. The excised skin of albino rats is made free of hair by shaving. The test was conducted on the unbraded skin of the rats. The skin was cleared using a rectified spirit and attached to the selected patch formulation. This was placed between the donor and receptor compartments of the Franz diffusion cell. Aliquots from the receptor compartment were collected and tested for the quantification of drug permeated via the excised skin[20,21].

Stability studies[19]

The purpose of the stability study was to provide evidence of the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. The formulation was selected on the basis of its physicochemical characteristics and drug content. The formulation was subjected to accelerated stability studies according to the International Conference on Harmonization guidelines. The most satisfactory formulation was sealed in aluminum foil and stored at 30 $\pm$ 2°C, 65 $\pm$ 5% H, 40$\pm$ 2°C, and 75 $\pm$ 5% RH for 4 weeks.

RESULTS

Preformulation Studies

Melting point determination

The melting point of nicorandil was 92°C which complied with the BP standards, indicating the purity of the obtained drug sample.

lambda max of nicorandil

The Nicorandil is soluble in water, soluble in alcohol, methyl alcohol, freely soluble in acetone, dimethyl formamide. The lambda max (λ_{max}) of nicorandil was 260 nm in 6.8 Phosphate buffer.

Calibration curve of Nicorandil

The standard curve yielded a straight line, which indicated that the drug obeyed Beers/Lambert's range in the concentration range of 5 – 40 μg/mL (Figure 1). The regression coefficient was found to be 0.9988.

Characterization of patches

The characterization of the patches is presented in Table 2. The drug content varied from 99.28 + 0.12 to 99.41 + 0.21%.

Table 2: Evaluation of patches

Formula code	Physical appearance	Thickness (mm)	Mass uniformity (mg)	Folding endurance	Drug content uniformity (%)	Moisture loss (%)
F1	Clear	0.35±0.51	12.23±1.11	125±0.32	99.28±0.12	7.486±0.185
F2	Clear	0.37±0.84	18.25±0.98	128±1	99.30±0.14	5.216±0.271
F3	Clear	0.38±0.78	24.78±0.67	131±0.88	99.35±0.17	6.48±0.248
F4	Clear	0.40±0.56	30.67±1.08	134±0.5	99.36±0.19	9.17±0.258
F5	Clear	0.42±0.65	35.76±0.99	136±0.98	99.37±0.2	6.813±0.0750
F6	Clear	0.43±0.56	41.23±0.67	140±0.67	99.41±0.21	4.55±0.227

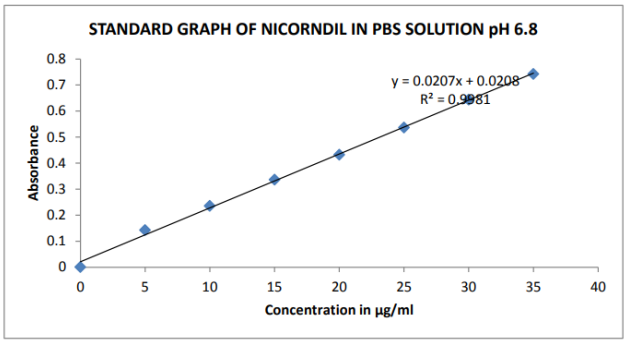

Fig. 1: Standard calibration curve for nicorandil in Phosphate buffer pH 6.8 at 260nm

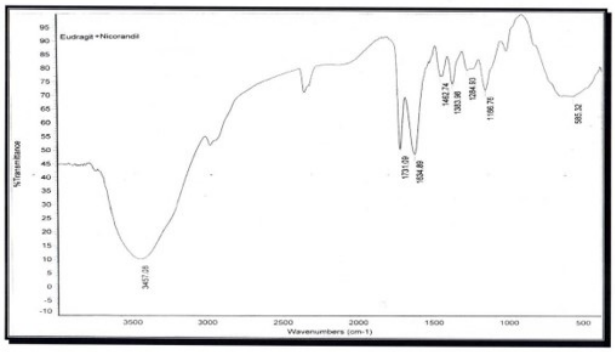

Fig. 3: FTIR Spectrum of physical blend

Drug polymer interaction (FTIR) study

The spectra of nicorandil, polymers, and the physical mixture of nicorandil and polymers showed that all characteristic peaks of nicorandil were present in the combination spectrum, thus indicating compatibility of the nicorandil and polymer (Figures 2 and 3).

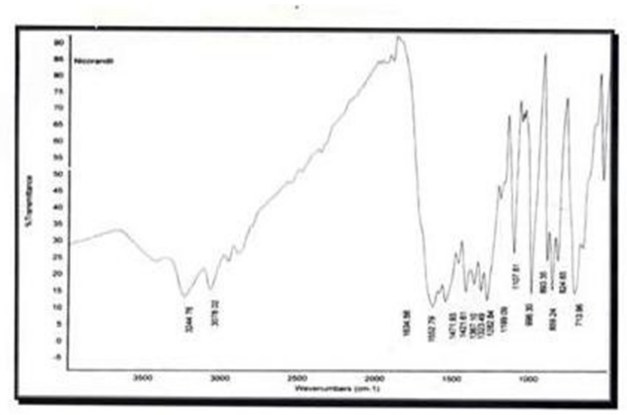

Fig. 2: FTIR Spectrum of Nicorandil pure drug

Surface morphology of Nicorandil patches

The SEM analysis revealed the surface morphology (Figures 4 and 5). SEM photographs of nicorandil patches indicated a uniform distribution of drug particles in the patches, and slight surface precipitation of the drug may be accounted for by unentrapped drug particles. The patches had a slightly uneven surface texture.

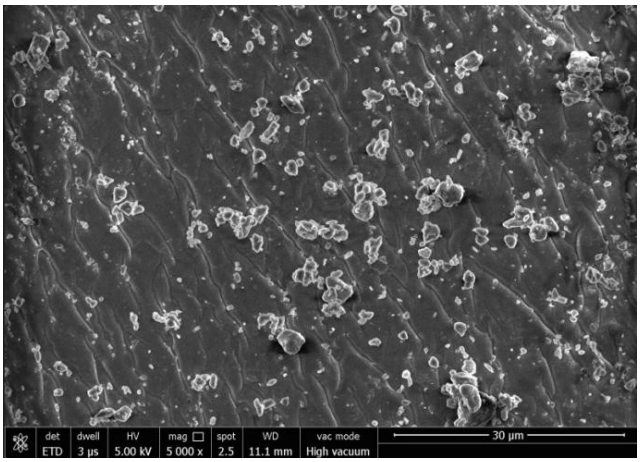

Fig. 4: SEM photograph of Nicorandil patches

In vitro release study

The in vitro performance of the nicorandil patches showed prolonged and controlled release of the drug from all formulations (Table 3 and Figure 6).

Table 3: In-vitro release datafrom Nicorandil patches

% Cum. Drug release*							
Time (hr)	**FI**	**F2**	**F3**	**F4**	**F5**	**F6**	**Pure drug**
0	0	0	0	0	0	0	0
0.5	16.22± 0.23	15.86± 0.66	16.01± 0.36	13.25± 0.54	10.1± 0.46	9.10±0.45	35.55± 0.54
1	22.04± 0.88	18.64± 0.56	19.01± 0.54	19.27± 0.47	17.84± 0.53	16.83±0.52	48.31± 0.67
2	29.45± 0.65	26.15± 0.78	27.2± 0.71	27.53± 0.33	23.72± 0.36	22.70±0.33	82.52± 0.25
3	36.55± 0.75	36.88± 0.64	35.82± 0.49	35.62±0.65	30.11± 0.29	29.10±0.28	95.42± 0.66
4	44.11± 0.66	41± 0.81	42.22± 0.57	39.53± 0.45	37.86± 0.78	36.85±0.68	-
5	49.55± 0.89	46.01± 0.67	47.15± 0.66	44.02± 0.58	42.01± 0.32	41.01±0.22	-
6	56.64± 0.67	57.26± 0.39	56.57± 0.59	50.21± 0.66	48.01± 0.36	47.01±0.26	-
7	63.26± 0.55	60.54± 0.81	59.26± 0.81	55.9± 0.39	52.01± 0.52	51.01±0.42	-
8	71.88± 0.48	65.31± 0.66	62.54± 0.54	63± 0.57	58.88± 0.45	57.78±0.35	-
9	79.82± 0.58	70.33± 0.54	68.8± 0.67	72.22± 0.77	65.21± 0.71	64.11±0.61	-
10	83.55± 0.69	74.41± 0.67	71.56± 0.58	76± 0.53	70.33± 0.54	69.33±0.51	-
11	86.45± 0.73	78.94± 0.55	76.32± 0.66	79.12± 0.45	75.01± 0.63	74.01±0.53	-
12	89.55± 0.62	87.66± 0.12	85.02± 0.26	82.79± 0.42	78.52± 0.62	77.42±0.52	-

All the values are expressed a mean ± SD Standard deviation (n=3)

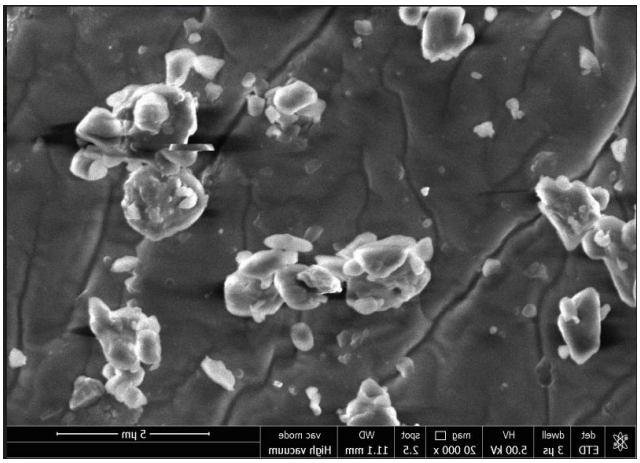

Fig. 5: SEM photograph of Nicorandil patches

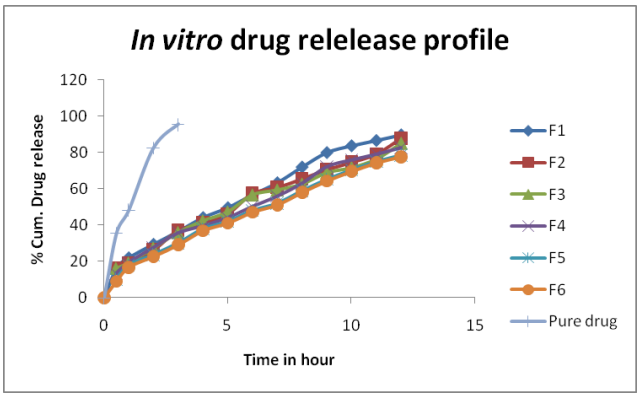

Fig. 6: In-vitro release profile

Ex vivo permeation study of selected formula F4

Ex vivo permeation studies of the selected formulation (F4) were performed using excised rat abdominal skin samples. An ex vivo permeation study of the selected formulation was carried out and compared with that of the pure drug, and the results were found to be in good agreement with those of the in vitro release study (Table 4 and Figure 7).

Table 4: Ex-vivo permeation study of optimized formula F4

Time (hrs)	%CDR	
	Nicorandil (pure)	**F2**
0.5	4.11± 0.004	10.24 ± 0.008
1	7.53± 0.002	17.32 ± 0.012
2	10.34± 0.012	22.56 ± 0.006
3	13.52± 0.016	29.12 ± 0.031
c4	18.16± 0.008	33.43 ± 0.022
5	22.52± 0.006	37.15 ± 0.009
6	26.92± 0.004	42.54±0.001
7	33.17± 0.012	49.15 ± 0.042
8	40.23± 0.024	54.21 ± 0.056
9	43.42± 0.034	60.89 ± 0.014
10	48.26± 0.012	68.55 ± 0.008
11	51.53± 0.006	75.41 ± 0.010
12	59.15± 0.005	88.11 ± 0.024

Stability studies

The selected formulation (F4) was subjected to accelerated stability studies at 25°C ± 2°C / 60% ± 5% RH and 40°C ± 2°C / 75% ± 5% RH, as shown in Table 5.

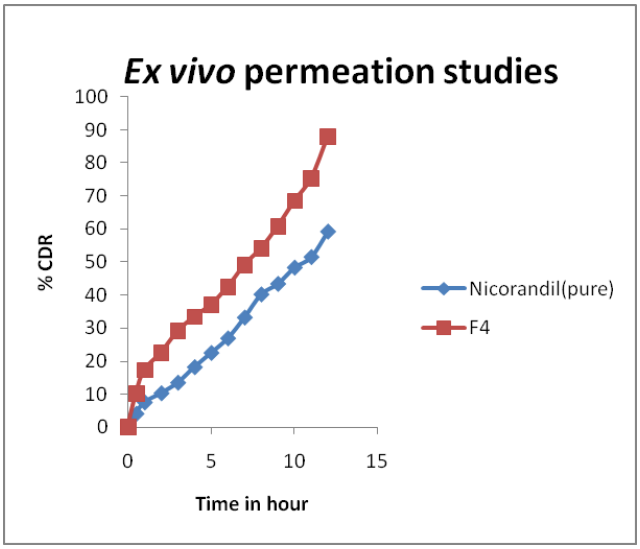

Fig. 7: Comparative Ex-vivo permeation profile

Table 5: The

No. of days	25 °C ± 2 °C / 60% ± 5% RH		40 °C ± 2 °C /75% ± 5% RH	
	Physical Appearance	Average % drug content	Physical Appearance	Average % drug content
0	No Change	99.01	No Change	98.55
15	No Change	99.12	No Change	98.11
30	No Change	98.88	No Change	98.45
45	No Change	98.99	No Change	98.13
60	No Change	98.96	No Change	98.19

DISCUSSION

The development of a transdermal patch is a suitable method to increase bioavailability. In the present study, we aimed to develop and evaluate transdermal patches of nicorandil for controlled drug delivery systems to prevent unwanted systemic side effects. Five formulations were prepared using Eudragit RL 100 as a polymer. A different transdermal patch formulation was observed for the evaluation parameters, and the F4 formulation was found to be the best formulation. The prepared nicorandil patches were evaluated for their appearance, uniformity, thickness, SEM analysis, drug content, in vitro release kinetics, and ex vivo permeation. The compatibility of the drug-polymer was checked using FTIR spectroscopy.

All patches were thin, elastic, smooth, flexible, and transparent; their uniformity and thickness were within the acceptable range. FTIR spectroscopy was performed to determine the compatibility between nicorandil and the Eudragit polymer used for the preparation of nicorandil patches. Characteristic peaks in the region were observed for combinations of drugs and polymers which were identical to those of the pure drug. This confirmed that there was no interaction between the drug and polymers.

F4 which contained 450 mg of nicorandil and 1500 mg of Eudragit RL-100, showed drug release for 12 h. Patches F4 were prepared by incorporating permeation enhancers and showed promising results. Transdermal skin irritation was tested in rats and no significant irritation was observed. SEM analysis showed that the patches had a slightly uneven surface texture. The in vitro performance of the nicorandil patches showed prolonged and controlled release of the drug from all formulations. An ex vivo permeation study of the selected formulation was carried out and compared with that of the pure drug, and the results were found to be in good agreement with those of the in vitro release study.

CONCLUSION

In this study, controlled nicorandil patches were developed to reduce side effects by regulating drug release through the skin. This was effectively accomplished using the solvent method with varying concentrations of Eudragit RL100. The F4 formulation exhibited a strong correlation with the in vitro drug release profile compared to that of the pure drug. Therefore, it can be inferred that the transdermal delivery system of nicorandil serves as a favourable alternative to oral and parenteral drug therapy because of its non-invasive and patient-friendly nature, resulting in sustained therapy over an extended duration.

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