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Formulation and evaluation of perindopril transdermal patch

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ABSTRACT

The objective of the present study was to develop matrix-type transdermal therapeutic systems of Perindopril using various hydrophilic and hydrophobic polymers as matrix formers. Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction, and no skin irritation was observed. The in vitro release study revealed that F4 formulation showed maximum release in 8 hrs. Formulation F4 was subjected to accelerated stability studies. The F4 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Perindopril have been developed. F1, F2, F3, F4 formulations showed the highest cumulative percentage drug release of 92.63%, 89.35%, 88.98%, 96.28% were obtained during in vitro drug release studies. The release of Perindopril appears to be dependent on the lipophilicity of the matrix. Moderately lipophilic matrices showed the best release. The predominant release mechanism of the drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the in vitro dissolution data the F4 formulation was concluded as an optimized formulation.

Keywords: Perindopril, Polymers, solvent casting technique, In-vitro drug release studies

INTRODUCTION

Discovering a new medicine is a very expensive and time-consuming process. However, re-designing the modules and means to transport medicine into the body is a less demanding and more lucrative task. The design of dosage form, whether a tablet, an injection or a patch, to deliver the right amount of medicine at the right time to the right target site becomes complicated if each medication were to be delivered in an optimal and preferred manner to the individual patient[1]. The medication may not be absorbed if it is released too slowly. If it is delivered too rapidly, the patient may suffer untoward effects and its desired effects may not last as long as needed. If the patient is expected to take the medicine more than two times a day, compliance will be adversely affected.[2] One of the solutions developed is transdermal drug delivery

systems which can deliver medicine via the skin portal to systemic circulation at a predetermined rate and maintain clinically effective concentrations over a prolonged period of time[3]. Transdermal drug delivery systems (TDDS), also known as patches, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin.[4] They are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin at a controlled rate to the systemic circulation (monk house, 1988). To deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical, and physicochemical properties of the skin are to be considered.[5] The transdermal route is an extremely attractive option for drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs that undergo extensive first-pass metabolism, drugs with narrow therapeutic windows, or drugs with short half-life which causes non-compliance due to frequent dosing. The foremost requirement of TDDS is that the drug possesses the right mix of physicochemical and biological properties for transdermal drug delivery.[6] The selection of drugs for transdermal drug delivery depends upon various factors. The purpose of this study was to develop formulations and systematically evaluate in-vitro diffusion studies of transdermal patches of Perindopril using different polymers.[7] Perindopril is a medicine used to treat high blood pressure and heart failure. It is also prescribed after a heart attack. Perindopril helps to reduce the risk of future strokes and heart attacks. It also improves your survival if you're taking it following a heart attack or heart surgery.[8]

MATERIALS

Perindopril was collected as a gift sample from Hetero labs, Hyd, polymers, and other excipients were purchased from AR Chemicals, Hyd.

METHODOLOGY

Compatibility studies

The drug-polymer compatibility was ascertained by subjecting the drug and homogenates of drug and polymer to Infrared spectrophotometric study.

Fourier Transform Infrared Spectroscopy (FTIR)

A proper design and formulation of a dosage form require consideration of the physical, chemical, and biological characteristics of both drug and excipients used in the fabrication of the product. Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive, and safe product. So before producing the actual formulation, compatibility of Perindopril with polymers and other excipients was tested using the Fourier Transform Infrared Spectroscopy (FT-IR). For this study, the potassium bromide (KBr) pellet method was employed. The samples were thoroughly mixed with dry powdered potassium bromide. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded. The application of infra-red spectroscopy lies more in the qualitative identification of substances either in pure form or in the mixtures and as a tool in the establishment of the structure. Since I.R. is related to covalent bonds, the spectra can provide detailed information about the structure of molecular compounds.[9]

Formulation design

Preparation of transdermal patches

Transdermal patches containing perindopril were prepared by the solvent evaporation technique. The drug perindopril was dissolved in a suitable solvent. Polymers HPMC k 5 M, and Eudragit RLPO were taken. These polymeric solutions are kept under a magnetic stirrer after 1 hr. get the viscous solution. After that drug adds to the polymeric solution. Sufficient care was taken to prevent the formation of lumps. PEG was taken as a plasticizer and permeation enhancer like DMSO was added to the mixture and mixed well. It was set aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned Petri plate (40cm^2), drying of patches was carried out in a vacuum oven at room temperature. Dried patches were packed in aluminum foil and stored in a desiccator for further evaluation[10].

Table 1: Formulation Design of Perindopril Transdermal Patches

S. No	Formulation code	Drug (mg)	EUDRAGIT RLPO	HPMC k5 M	PEG	DMSO
1	F1	200	200	-	1ml	0.1ml
2	F2	200	400	-	1ml	0.1ml
3	F3	200	-	200	1ml	0.1ml
4	F4	200	-	400	1ml	0.1ml

Evaluation of transdermal formulation

Physicochemical evaluation

Physical appearance

All the prepared transdermal films were observed for color, clarity, flexibility, and smoothness.

Folding endurance

The folding endurance of the patches was determined by repeatedly folding at the same place till they broke. The number of times the patch could be folded at the same place without breaking is the folding endurance. This was repeated on all the patches three times and the mean values plus standard deviation were calculated[11].

The thickness of the film

The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film[12].

Weight uniformity

The prepared patches are to be dried at 60^0C for 4hrs before testing. A specified area of 4.52 cm^2 of the patch is to be cut in different parts of the patch and weighed in the digital balance. The average weight and standard deviation values are to be calculated from the individual weights.[13]

Flatness

Flatness was determined by randomly selecting five longitudinal strips that were cut out from a mediated patch of each formulation; the length of each strip was measured before and after being kept at room temperature for 30 minutes. Variation in length due to non-uniformity of flatness was measured by determining percent constriction, with 0% constriction as 100% flatness.[14]

$$\text{Percent constriction} = \frac{\text{Final length} - \text{Initial length}}{\text{Initial length}} \times 100$$

Drug content

The formulated transdermal films were assayed for drug content in each case. Three patches from each formulation were assayed for the content of the drug. Each formulation was cast in triplicate and one film from each was taken and assayed for the content of the drug.[15]

Procedure

The transdermal films (4.52 cm^2) were added to the conical flask containing 100 ml of phosphate buffer pH 7.4. This was then stirred with a magnetic bead at 400 rpm for 2 hrs. The contents were filtered and the filtrate was analyzed spectrophotometrically for drug content at nm. Similarly, a blank was prepared from transdermal films without drugs.[16]

Moisture absorption studies

The films were weighed accurately and placed in a desiccator containing aluminum chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.[13]

$$\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss studies

Three films were weighed individually and kept in a desiccator containing calcium chloride at 37^0C for 24 hrs. Then the final weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.[14]

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

In vitro release study

The *in-vitro* study of drug permeation through the Dialysis membrane was performed using a modified Franz-type glass diffusion cell. The modified cell having a higher capacity is (10 ml) is used to maintain sink condition. The samples were analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.[15]

The percentage of drug release was determined using the following formula.

$$\text{Percentage drug release} = \frac{\text{Da}}{\text{Dt}} \times 100$$

Where Dt = Total amount of the drug in the patch

Da = The amount of drug released

Conditions

Medium: Phosphate buffer pH 7.4 containing 0.5% SLS
RPM: 200
Temperature: 37 ± 0.5^0C
Time intervals: 1, 2, 3, 4, 5, 6, 7, 8 hours

Stability studies

Optimized medicated patches were subjected to short-term stability testing. The transdermal films were sealed in aluminum foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 30 Days as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every.[16]

RESULTS AND DISCUSSION

In the present study, 4 formulations with variable concentrations of polymer were prepared and evaluated for physic-chemical parameters, in vitro release studies, and stability studies.

Drug - excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected lipid and other excipients was evaluated using the FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-polymer mixture, which confirmed the absence of any chemical interaction between the drug, polymers, and other chemicals.

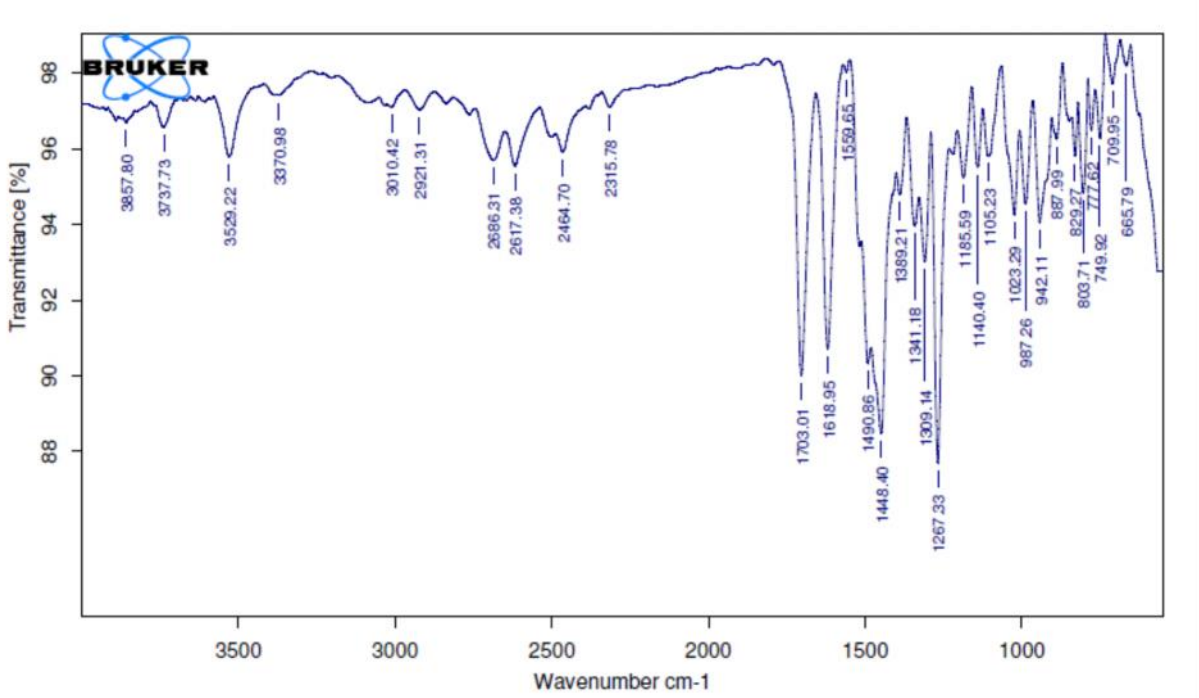

Fig 1: FT-IR Sample for Perindopril

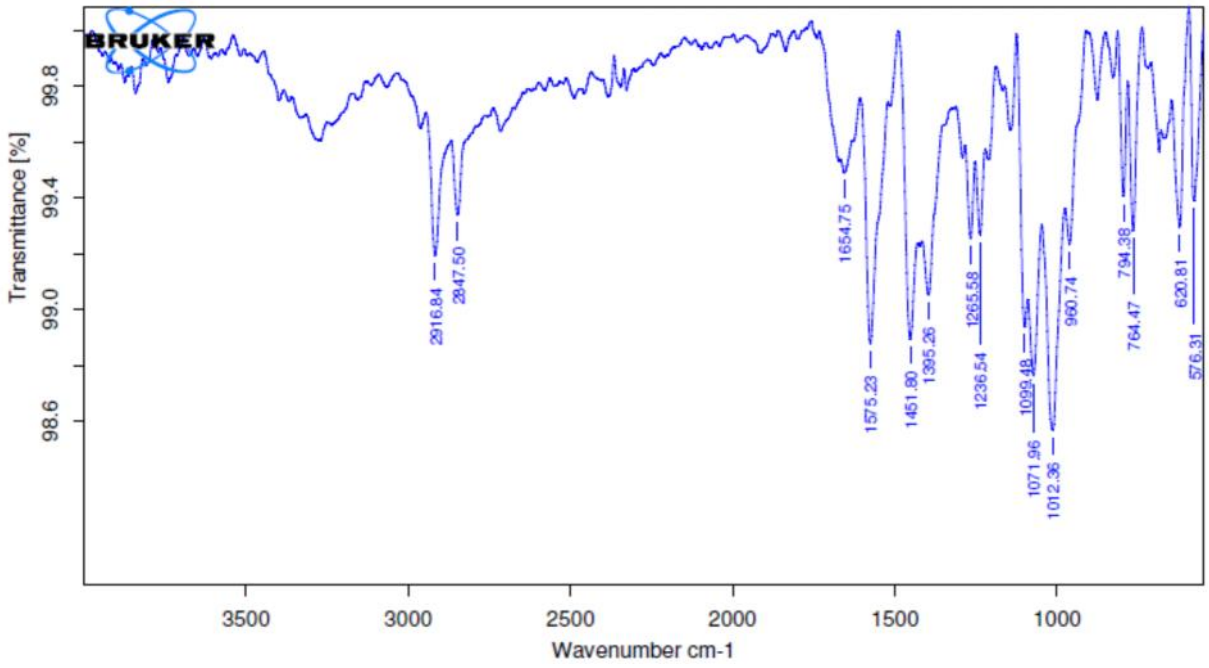

Fig 2: FT-IR Sample for Optimized Formulation

Evaluation of Transdermal formulation

Physical appearance

The prepared patches were found to be uniform, smooth, flexible, and homogenous.

Folding endurance

The folding endurance numbers of all the Perindopril patches are 287– 292. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high mechanical property. The folding endurance number was increased with increasing the HPMC content. These results indicated that the patches would not break and maintain their integrity with general skin folding when applied.

The thickness of the film

Thickness was changed from batch to batch in individual strips of medicated patch carry uniform thickness, which indicates that total medicated patch carry uniform thickness.

Weight uniformity

The mean weights of all the prepared patches. The F4 formulation patches showed maximum weight.

Drug content

The drug content analysis of the prepared formulations has shown that the process employed to prepare the patches was capable of giving uniform drug content with minimum batch variability. All the patches were found to have drug content in the range of 90 – 101%. So the method employed i.e. solvent evaporation method is satisfactory for the preparation of Perindopril transdermal patches.

Table 2: Physicochemical evaluation of Perindopril patches

Formulation code	Weight (mg)	Thickness (µm)	Folding endurance	Drug content (%)
F1	251	200	292	101
F2	245	213	290	97.39
F3	265	214	288	92.45
F4	312	219	287	98.86

Table: 3 Physicochemical evaluation of Perindopril patches

Formulation code	Moisture loss	Moisture Absorption
F1	4.45	6.65
F2	4.34	6.65
F3	4.52	6.26
F4	4.75	6.28

In vitro release study

Phosphate buffer pH 7.4 was used as a medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.998. The drug release profiles of Perindopril patches containing different ratios of polymers HPMC, Eudragit RLPO. It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and content.

Table: 4 *In vitro* drug release profiles of Perindopril transdermal patch (F1-F4)

Time (hrs)	% Cumulative drug released			
	F1	F2	F3	F4
0	0	0	0	0

1	13.56	10.65	13.48	11.79
2	22.72	19.27	26.50	24.67
3	34.94	25.4	31.71	26.627
4	41.16	30.28	34.36	30.18
5	57.88	43.63	56.25	46.71
6	76.93	63.49	70.30	69.48
7	88.98	71.26	79.96	82.59
8	92.63	89.35	88.98	96.28

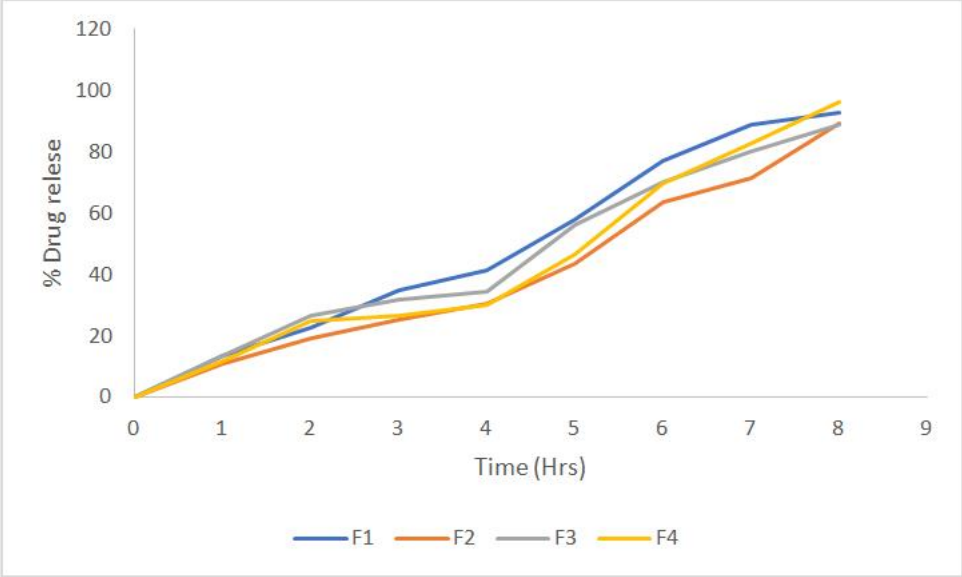

Fig: 3 Drug release formulations

Stability studies

Optimized formulations F4 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance, and flexibility for three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies.

Table: 5 Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 30 days

Time in days	Drug content (%)	Folding endurance	Physical appearance	% Cumulative drug release
0	98.86	285	No change in color	96.28
30	98.78	281	Slight yellowish color	96.12

CONCLUSION

Its oral therapy is often associated with several problems like poor bioavailability, frequent dosing leading to the patient in compliance, and other systemic & local adverse effects. The transdermal drug delivery system provides a means to controlled drug release as well as reduce the intensity of action and thus reduces the side effects associated with its oral therapy. Therefore, Perindopril was chosen as a model drug and an attempt was made to deliver Perindopril in the transdermal dosage form. Characterization of Perindopril was done by performing the melting point, UV spectroscopy, and IR spectroscopy. IR spectrum of the pure drug was compared with that of physical mixture of drug with all excipients used in the study. The results showed that there was no drug-excipient interaction. The melting point was found to be 188^{0}C

and the UV spectral analysis of the drug solution indicated that λ_{max} value as 213nm. Transdermal therapeutic systems of Perindopril were prepared by solvent casting method by using different polymers. In the present study a total of F4 formulations were prepared, all the formulated patches were evaluated for physicochemical and mechanical properties. Formulated patches also evaluated for moisture absorption, moisture loss studies and stability study results revealed that the obtained results were within the accepted limits. *In vitro* release study was performed using Franz diffusion cell

The following conclusions could be drawn from the results:

- Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction, and no skin irritation was observed.
- The F4 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Perindopril have been developed.
- F1, F2, F3, F4 formulations showed the highest cumulative percentage drug release of 92.63%, 89.35%, 88.98%, 96.28% were obtained during *in vitro* drug release studies after 8 hrs.
- Based upon the *in vitro* dissolution data the F4 formulation was concluded as an optimized formulation.

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