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Research Article

FORMULATION EVALUATION AND *IN VITRO* PERMEATION STUDIES OF TRANSDERMAL NIFEDIPINE FROM MATRIX TYPE PATCHES

ARUN RAJ.R

University College of Pharmacy, Mahatma Gandhi University RIMSR, Kottayam, Kerala, India. Email: arunraj2486@gmail.com

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ABSTRACT

Objective: The purpose of this research work was to develop and evaluate matrix type transdermal therapeutic system containing drug nifedipine with different ratios of four polymers by the moulding technique.

Methods: The physicochemical parameters such as physical appearance, folding endurance, thickness, weight uniformity, percentage moisture uptake, percentage moisture content, percentage drug content, percentage flatness and percentage of swelling index were evaluated. *In vitro* permeation studies of formulations were performed by using Franz diffusion cells and data were fitted to various kinetic models.

Results: Folding endurance test results indicated that the patches would maintain their integrity with general skin folding. For all the formulation the thickness varied between 0.12 to 0.15mm. The moisture uptake studies revealed that all the patches were having the low moisture uptake and moisture content. Drug content among the batches were ranged from 98.6% to 99.8%. The flatness study showed no amount of constriction was observed. Percentage of swelling index of all the polymers were between 0.5 - 13.9%. Among the formulations prepared F4, showed a better combination for the controlled release. Nifedipine patches follow zero order kinetics of permeation.

Conclusion: Results from various evaluations suggested that matrix type nifedipine patches could be used as transdermal drug delivery devices.

Keywords: Nifedipine, Transdermal drug delivery, Matrix type patches, Moulding technique.

INTRODUCTION

In the past, the delivery of medications transdermally to a patient has been limited to administration by transcutaneous injection or by transdermal migration from a patch placed on the outer surface of the patient's skin. It has recently become evident that the benefits of intra venous can be duplicated using skin as a drug delivery route[1]. Transdermal drug delivery systems (TDDS) allow delivery of contained drug into the systemic circulation via permeation through skin layers at a controlled rate. These systems are easy to apply and remove as and when desired. This approach of drug delivery is more pertinent in case of chronic disorders, such as hypertension, which require long-term dosing to maintain therapeutic drug concentration[2].

Transdermal drug delivery systems, in comparison to conventional pharmaceutical dosage forms, offer many advantages, including improved systemic bioavailability of active pharmaceutical ingredients, such as improving patient compliance in longterm therapy, bypassing first-pass metabolism, sustaining drug delivery, maintaining a constant and prolonged drug level in plasma, minimizing inter- and intra patient variability, fewer administration frequency, longer duration of therapeutic action, reduction of side effects and steady drug delivery profile, etc[3,4].

It has been necessary for the TDDS to meet two requirements. First, the method must provide for extended containment of the drug and any carrier while placed on the patient's skin, in a form that does not lend itself either to contamination of the medication and carrier or to loss of the medication and carrier. Second, the systems employed must provide for a regulated and predictable rate of transfer of the medication (with or without the carrier) from the containment device into and through at least some layers of skin to where the medication will be dispersed throughout the affected area of the body[5].

METERIALS AND METHODS

Materials

The following materials were used: Nifedipine (Medopharn Laboratories, Banglore), Polyvinyl alcohol and Poly vinyl pyrrolidone (Sigma Aldrich, Steinheim), Ethyl cellulose and Glycerin (SD Fine Chemicals, Mumbai), Hydroxypropyl methyl cellulose (Himedia Laboratories, Mumbai), Tween 80 (Indian research products, Mumbai), chloroform (Qualigens fine chemicals, Mumbai).

Methods

Drug–polymer compatibility studies[6]

In the preparation of transdermal patches of nifedipine, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between nifedipine and the selected polymers. Potassium bromide was mixed with drug and/or polymer in 9:1 ratio and the spectra were taken. FT-IR spectrum of nifedipine was compared with FT-IR spectra of polymers.

Formulation of transdermal patches

General method of preparation of transdermal patches

In the present study, matrix type transdermal patches of nifedipine were prepared by moulding techniques. A flat circular glass moulds having diameter 4.5cm and height of 1cm with a total surface area of 15.91cm^2 was fabricated for this purpose.

Preparation of casting solutions[7,8]

The polymeric solution were prepared by dissolving the polyvinyl alcohol (PVA) and poly vinyl pyrrolidone (PVP) combination in water in the ratio 8:2, 5:5, 0:8. Similarly the polymeric solution of hydroxypropyl methyl cellulose (HPMC) and ethylcellulose (EC) combination were prepared by dissolving the combination in alcohol: chloroform mixture (1:1) in the ratio 2:2, 3:1, 0:3. Glycerine was used as plasticizer and dimethyl sulfoxide (DMSO) as penetration enhancers. Weighed amount of drug was dispersed in each of the polymeric solutions while stirring to ensure the uniform distribution of drug. It was placed aside without any disturbances to allow the entrapped air to bubble out.

Evaluation of transdermal patches

Physical appearance [9]

All the transdermal patches were visually inspected for color, clarity, flexibility, and smoothness.

Folding endurance

A strip of film (4 × 3 cm) was cut evenly 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 gave the value of the folding endurance.

Table 1: Compositions of transdermal patches of Nifedipine

Materials	F1	F2	F3	F4	F5	F6
Nifedipine(mg)	10	10	10	10	10	10
Glycerin in %w/w	20	20	20	20	20	20
DMSO % w/w	5	5	5	5	5	5
PVA in parts	8	5	-	-	-	-
PVP in parts	2	5	8	-	-	-
HPMC in parts	-	-	-	2	3	-
EC in parts	-	-	-	2	1	3

Thickness of the films

The thicknesses of the drug-loaded polymeric films were measured at 5 different points using a digital micrometer. The average and standard deviation of 5 readings were calculated.

Weight uniformity

The films of different batches were dried at 60°C for 4 hours before testing. Five patches from each batch were accurately weighed in a digital balance.The average weight and the standard deviation values were calculated from the individual weights.

Average weight of each patches = total weight of 5 patches/ 5

$$\text{Standard deviation} = \sqrt{\frac{\sum (x - X)^2}{n-1}}$$

Where x = weight of individual patch.

X = average weight.

n = number of patches.

Percentage moisture uptake

The weighed films were kept in a desiccator at room temperature for 24 hours and then exposed to 84% relative humidity using a saturated solution of potassium chloride.Finally, the films were weighed and the percent moisture uptake was calculated using the formula

Percentage moisture uptake = [Final weight - Initial weight/Initial weight] × 100

Percentage moisture content

The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hours.The films were again weighed and the percentage moisture content was calculated using the formula

Percentage moisture content = [Initial weight - Final weight/Final weight] × 100

Drug content

Transdermal patches of specified area (3.066 cm^2) was cut into small pieces and taken into a 50 ml volumetric flask and 25 ml of phosphate buffer pH 7.4 was added, gently heated to 45°C for 15 minutes, and kept for 24 hours with occasional shaking. Then, the volume was made up to 50 ml with phosphate buffer of pH 7.4. Similarly, a blank was carried out using a drug-free formulation. The solutions were filtered and the absorbance was measured at 238nm.

Flatness

Three longitudinal strips were cut out from each film: 1 from the center, 1 from the left side, and 1 from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

The physico- chemical parameters of the transdermal patches were shown in table: 2.

Swelling Ratio Measurement[10]

Preparation of Disc-Like Specimens

Discs of the polymers used were prepared by compressing 500 mg of powder using flat-faced punches 12 mm in diameter to yield a hardness of 100 N ± 10. Before swelling tests, the diameter and height of each tested disc were measured.

Swelling Studies

Swelling studies were performedby placing the polymeric discs in petridishes at 37°C and measuring their thickness as a function of time during swelling. The swelling ratios of different polymers were given in the figure: 2.

***In vitro* drug release studies**

The study was carried out in the USP XXXIV Type I apparatus using 900ml phosphate buffer (pH 7.4) solution and rotated at constant speed (50 rpm) and the temperature of the medium was maintained at 37°±0.5°C for 8 hours. The transdermal patch was mounted on the disc and placed at the bottom of the dissolution vessel. An aliquot of the sample was periodically withdrawn at the regular time intervals and an equal volume was replaced with fresh dissolution medium. The samples were filtered and diluted to a suitable concentration with respective medium. Absorbance of these solutions was measured at 238 nm using UV-Visible spectrophotometer. The percentage drug released at different time intervals were calculated.

***In vitro* permeation studies**

In vitro permeation studies were performed on Franz diffusion cells with an effective sectional area of 3.14 $cm^2$and 15 ml of receiver chamber capacity. The cellophane membrane was tightly secured between the donor and receptor compartments. The upper surface of the membrane was exposed to solution of drug formulation. The receptor compartment was filled with isotonic phosphate buffer pH 7.4. The whole assembly was kept on a magnetic stirrer and solution in the receptor compartment was constantly and continuously stirred using a magnetic bead. An aliquot of the sample was periodically withdrawn at the regular time intervals and an equal volume was replaced with fresh dissolution medium. Absorbance of these solutions was measured at 238 nm using UV-Visible spectrophotometer.

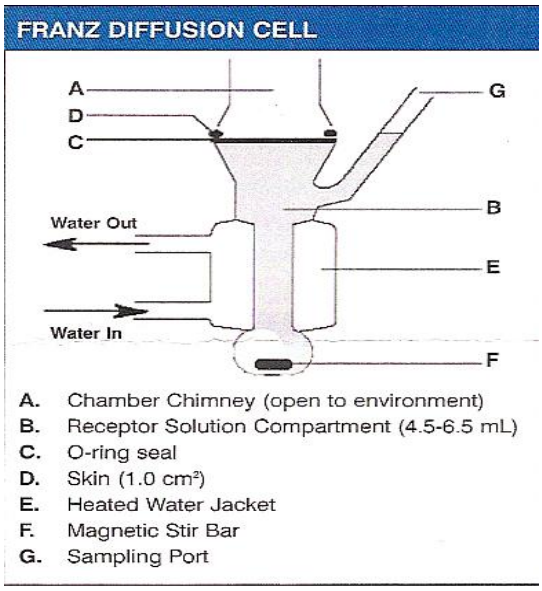

Fig. 1: Franz diffusion cell

Kinetics of *in-vitro* drug release

To study the release kinetics of *in-vitro* drug release, data obtained from in-vitro release study were plotted in various kinetic models: Zero order as % drug released Vs time, First order as log % drug retained Vs time, Higuchi as % drug released Vs √time, Korsmeyer-Peppas as log %drug released Vs log time and Hixson-Crowell as (% drug retained)$^{1/3}$Vs time. By comparing the r-values obtained, the best-fit model was selected.

Skin irritation test

A primary skin irritation test was performed on six healthy rabbits, weighing between 2 to 3.5 kg. The patch of area 3.14 cm^2 was used as a test patch. The dorsal surface of rabbits was cleared well and the hair was removed by using a depilatory preparation. The skin was cleared with rectified spirit. The transdermal patch was placed on the dorsal surface of the abdominal skin with the help of an adhesive tape. The patches were removed after 24 hr and the skin was examined for erythema and edema.

Stability studies

Stability is defined as the extent, to which a product retains with in specified limits and throughout its period of strong and uses i.e. shelf life. Stability studies were carried out an optimized formulation according to International Conference on Harmonization (ICH) guidelines.

All the selected formulations were subjected to a stability testing for 6 weeks as per ICH norms at a temperature (40ºC). All selected formulations were analyzed for the moisture content, moisture uptake, thickness, weight variation, folding endurance, flatness, % drug content, and *in vitro* drug release study by procedure stated earlier.

RESULTS AND DISCUSSION

Drug–polymer compatibility studies

The IR spectra obtained from the mixture of polymers and drug was matching with the spectra of the pure drug. There was no appearance or disappearance of any characteristic peaks, which confirmed the absence of chemical interaction between the drug and the polymer used.

Table 2: Physico-chemical parameters of the nifedipine transdermal patches

Parameters	F1	F2	F3	F4	F5	F6
Physical appearance	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent	flexible, smooth and transparent
Folding endurance	324	335	349	226	238	153
Thickness (mm)	0.14± 0.004	0.15± 0.007	0.14± 0.006	0.14± 0.012	0.13± 0.009	0.12± 0.001
Weight variation(g)	0.56 ±0.02	0.42 ± 0.06	0.20 ± 0.1	0.36 ± 0.08	0.35 ± 0.04	0.41 ± 0.01
%moisture uptake	22.3	28.7	77.1	28.5	29.1	1.6
%moisture content	3.2	3.4	4.2	3.6	3.8	0.8
%Drug content	98.9	99.6	99.8	99.2	98.6	98.8
%Flatness	99.9	99.9	99.8	99.9	100	100

Folding endurance test results indicated that the patches would not break and would maintain their integrity with general skin folding when applied. Folding endurance was in the range of 153 to 349, transdermal patch F6 representing the least value, due to the brittle nature of EC and F3 has the maximum folding endurance due to the hydrophilic nature. For all the formulation the thickness varied between 0.12 to 0.15mm. The low values for standard deviation indicate physical uniformity of the patches. The weights obtained by the formulated transdermal patches were between 0.20g and 0.56g. The moisture uptake studies revealed that all the formulated transdermal patches were having the low moisture uptake and moisture content when compared with formulation F3. The reason for increase in moisture uptake and content for F3 may be attributed to the hygroscopic nature of the polymer, where F6 transdermal patches has the least moisture content and uptake due to the hydrophobic nature of the polymer. Good uniformity of drug content among the batches were observed with all formulations and ranged from 98.6% to 99.8%. The flatness study showed that all the formulations had the same strip length before and after their cuts, indicating ~100% flatness. Thus, no amount of constriction was observed; all patches had a smooth, flat surface; and that smooth surface could be maintained when the patch was applied to the skin.

Among the transdermal patches prepared formulation F4 containing HPMC and EC at 2:2 ratios with DMSO as penetration enhancer showed better combinations for the controlled release of nifedipine. This might be attributed to the nature of polymer, plasticizer and permeation enhancer used.

The release data obtained was subjected to zero order, first order, Higuchi's, Kosermayer's, Hixson-Crowell in order to establish the drug release mechanisms and kinetics of drug release from the tablet formulations. Criteria for selecting the most appropriate model were based on the best goodness of fit indicated by the value of regression coefficient(r). The *in vitro* release profiles of drug from all the formulations could be best expressed by zero order equation. Skin irritation test performed on rabbit the results of skin irritation test were showed absence of erythema and edema for test patches compare with control.

Stability studies

The results of accelerated stability studied indicated that there was no significant change in the patches. The drug content was found to be within 100±5% for all the formulations at the end of 90 days. FTIR analysis suggested that there was no significant degradation or changes taking place in the patches during the study period.

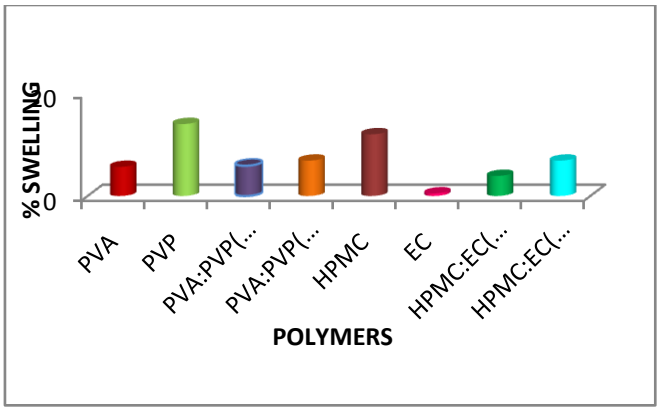

Fig. 2: Percentage swelling index of Polymers used in transdermal patches.

Percentage of swelling index for all the polymers used in transdermal patches were between 0.5 - 13.9%. The order of increasing swelling index of the polymers are as follows, PVP > HPMC > PVA > EC.

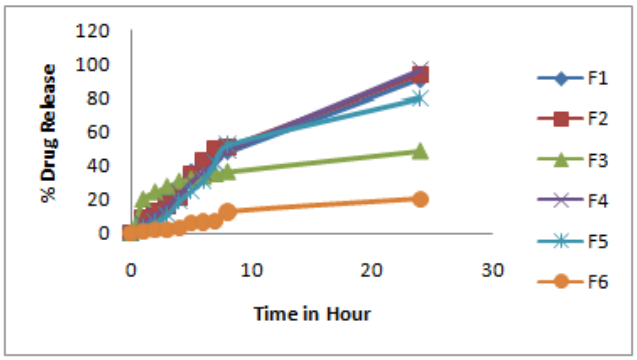

Fig. 3: *In vitro* dissolution profile of formulated transdermal patches F1- F6.

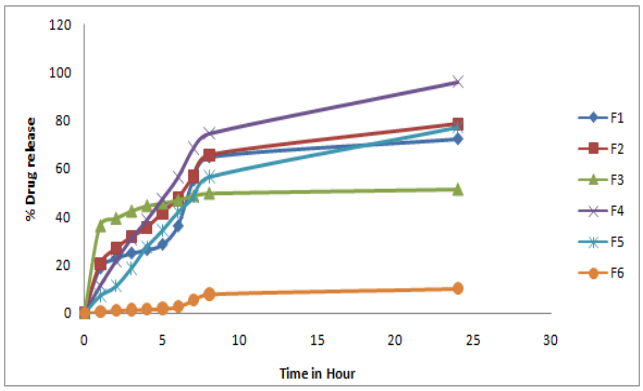

Fig. 4: *In vitro* permeation profile of formulated transdermal patches F1- F6.

CONCLUSION

In the present investigation an attempt has been made to design and develop the formulation of nifedipine patches using different ratios of polymers by the moulding technique. Nifedipine was successfully formulated as controlled release transdermal patches, which prevents the frequency of administration and gives good patient compliance. All the evaluation parameters obtained from the formulations were found to be satisfactory. Based on the observation, it can be concluded that the attempt of formulation and evaluation of the nifedipine patches was found to be successful in the release of the drug for an extended period.

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