ISSN 2582 – 6050

Available Online at www.ijpba.info
International Journal of Pharmaceutical & Biological Archives 2024; 15(1):27-32

RESEARCH ARTICLE

Formulation and Evaluation of Transdermal Patches of Nitrendipine Eudragit RLPO and RSPO Using Rate Controlling Polymers

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Received: 14 January 2024; Revised: 02 February 2024; Accepted: 05 March 2024

ABSTRACT

This study aims at formulation evaluation of nitrendipine transdermal patch to mitigate hypertension. In total, six formulations of transdermal patches were prepared, and they were evaluated for various parameters. The thickness of the patch ranged from 89 ± 2 to 98 ± 6 µm. The folding endurance was observed to be extended from 178 ± 5 to 225 ± 7. The % moisture content was varied from 5.12 ± 0.22 to 5.69 ± 0.32% while the moisture uptake ranged from 3.12 ± 0.32 to 3.96 ± 0.23%. In addition, the tensile strength was estimated as 0.45 ± 0.03 to 0.58 ± 0.03 kg/cm^2. The % drug content was found to be maximum for F2 formulation which is about 99.12 ± 0.23% and lowest in the case of F1 formulation which is about 96.65 ± 0.15%. The *in vitro* % drug release was noticed to be 99.45 % in F1 and F6 formulations. Although the % drug release is better for F1 and F6, the F2 formulation is considered to be more superior and ideal by comparing between above-mentioned parameters.

Keywords: Hypertension, Nitrendipine, transdermal drug delivery system, transdermal patch

INTRODUCTION

The most prevalent modifiable risk factor for death and disability is hypertension. Other modifiable risk factors include stroke, heart failure, accelerated coronary and systemic atherosclerosis, chronic kidney disease, lowering blood pressure with antihypertensive medications, reducing the damage to target organs, and lowering the prevalence of cardiovascular disease. Typically, hypertension comes on gradually over time. A person's risk of high blood pressure increases if they are overweight, have a family history of hypertension, do not keep a healthy diet, or are older than 60. The use of oral contraceptives, stress, renal illness, diabetes, sleep apnea, smoking, excessive alcohol consumption, and a diet high in sodium, low in potassium, and Vitamin D are among the factors that contribute to hypertension (Schiffrin, 2001; Chiang *et al*., 1969).

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One of the following four groups of antihypertensive medications – ACE inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide-type diuretics – may be used as the first agent. These treatments all lower the risk of cardiovascular events. A meta-analysis of 147 randomized controlled trials involving 464,000 hypertensive patients showed that all major anti-hypertensive drug classes (diuretics, angiotensin-converting enzyme inhibitors, ARBs, beta-blockers, and CCBs) cause a reduction in CAD event and stroke for the reduction in blood pressure, with the exception of the major effect of beta blockers administered after MI reduced CAD event and CCBs reduced stroke. The efficacy and tolerability of antihypertensive medications should be taken into consideration while treating adult hypertension, according to the 2011 ACC/AHA hypertension guidelines (Arguedas *et al*., 2009; Oparil and Schmieder, 2015).

A more modern method of delivering drugs is called a controlled-release drug delivery system,

which releases the medication into the bloodstream at a predefined pace. These solutions assisted in overcoming the multidose therapy-related negative effects of the traditional drug system. For a variety of reasons, the development of technology that uses the skin as a port of entry to release drugs into the systemic circulation at a controlled rate has gained popularity (Keleb *et al*., 2010).

Adhesive drug-containing devices with a specific surface area, known as transdermal drug delivery systems (TDDS), apply a predetermined dosage of medication to intact skin at a preprogrammed rate. Transdermal delivery has grown in significance in the past few years. Potential benefits of the TDDS include avoiding hepatic first-pass metabolism, sustaining stable blood levels for an extended period of time, which can reduce the need for frequent doses, enhanced bioavailability, less gastrointestinal discomfort, and increased patient compliance (Gaikwad *et al*., 2013).

Transdermal patch dosage form of transdermal therapeutic system (TTS) has been commercially available since the early 1980s. Comparing this approach to alternative traditional systems, there are numerous important clinical advantages. As a result, the TTS has special clinical importance in the long-term management and prevention of chronic illnesses such as hypertension. While certain antihypertensive medications have already been developed and tested as transdermal patches, the majority are still untested. In the near future, transdermal formulation of antihypertensive drugs is a promising development (Rastogi and Yadav, 2012).

A transdermal patch is an adhesive patch with medication that is applied topically to transfer a predetermined amount of medication through the skin and into the bloodstream. This frequently encourages the body's wounded area to mend. Compared to other methods of medication delivery, such as oral, topical, intravenous, and intramuscular, a transdermal drug delivery route has the advantage of allowing for controlled medication release into the patient through the patch. This is typically achieved by either a porous membrane covering a reservoir of medication or by body heat melting thin layers of medication embedded in the adhesive (Wokovich *et al*., 2006).

The commonly used drug for hypertension is nitrendipine. Nitrendipine is a Calcium Channel Blocker (CCB) with a vasodilator properties. It is a moderately natriuretic agent instead of sodium retentive, which sets it apart from other CCBs. It is also an excellent antihypertensive agent. Nitrendipine prevents the inflow of extracellular calcium across the smooth muscle cell membranes of the heart and blood vessels by rupturing the channel, blocking ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum. Reduction of intracellular calcium causes myocardial smooth muscle cell contractile processes to be inhibited, which dilates coronary and systemic arteries, increases oxygen delivery to the myocardial tissue, reduces total peripheral resistance, lowers systemic blood pressure, and reduces afterload (Santiago and Lopez, 1990; Scriabine, 1984).[1-10]

MATERIALS AND METHODS

Nitrendipine was obtained as a gift sample from the pharmaceutical industry. Chemicals such as Eudragit RLPO and RSPO, chloroform, and methanol with PEG 600, HPMC, Ethyl Cellulose, and Glycerin were obtained from Loba Chemie Pvt. Ltd. Mumbai.

Preparation of Blank Patches

Accurately weighed polymers were taken in combination and dissolved in respective solvents (chloroform and methanol in the ratio of 1:1 v/v) then poured in Petri dish with glycerin on the plain surface. Then film was dried overnight at room temperature.

Preparation of Rate Controlling Membrane

Eudragit RLPO and RSPO were used for the preparation of rate-controlling membranes. Polymers were dissolved in chloroform and methanol with PEG 600 as plasticizer (Table 1). Then, solution was then poured into a glass Petri dish. The solvent was allowed to evaporate under room temperature for 24 h (Prajapati *et al*., 2011).

Table 1: Preparation of matrix-type transdermal patches

Formulation Code	Drug (mg)	HPMC (mg)	RLPO (mg)	RSPO (mg)	Ethyl cellulose (mg)	Total polymer weight (mg)	Plasticizer % w/w	Permeation Enhancer % w/w
F1	240	250	150	-	100	500	0.5	10
F2	240	300	100	-	100	500	0.5	10
F3	240	350	50	-	100	500	0.5	10
F4	240	250	-	150	100	500	0.5	10
F5	240	300	-	100	100	500	0.5	10
F6	240	350	-	50	100	500	0.5	10

Plasticizer % w/w of total polymer PEG 6000 (mL). Permeation Enhancer % w/w of total polymer (Methanol, chloroform) mL

Table 2: Evaluation parameters

S. No.	Formulation code	Thickness* (µm)	Folding Endurance* (times)	% Moisture content*	% Moisture uptake*	Tensile strength (kg/cm^2)	% Drug content
1	F1	92±5	185±8	5.58±0.15	3.45±0.15	0.45±0.03	96.65±0.15
2	F2	89±2	225±7	5.12±0.22	3.12±0.32	0.48±0.05	99.12±0.23
3	F3	96±3	186±2	5.69±0.32	3.85±0.14	0.52±0.04	97.85±0.22
4	F4	98±6	205±6	5.48±0.15	3.96±0.23	0.58±0.03	96.65±0.18
5	F5	95±5	178±5	5.36±0.16	3.47±0.25	0.49±0.02	98.12±0.16
6	F6	97±4	165±8	5.47±0.22	3.65±0.36	0.52±0.04	97.66±0.15

*Average of three determinations (n=3, mean±S.D.)

Table 3: *In vitro* % permeation profile of nitrendipine in formulation F1-F6

Time (h)	% of drug release						
	F1	F2	F3	F4	F5	F6	Pure drug
0.5	26.65	24.45	22.32	36.65	32.25	30.25	46.65
1	43.32	36.65	30.25	48.85	43.32	42.12	69.98
2	68.85	53.32	45.65	59.98	53.32	50.36	96.65
4	76.65	68.85	55.56	68.85	63.32	60.32	-
6	83.32	76.65	63.32	89.98	85.45	83.32	-
8	98.12	89.98	74.45	96.65	93.36	90.32	-
10	99.12	94.45	88.85	98.85	98.78	98.85	-
12	99.45	99.15	93.32	99.12	99.19	99.45	-

Preparation of Matrix Type Transdermal Patches

Transdermal patches are composed of different polymers HPMC, ethyl cellulose, Eudragit RLPO, and Eudragit RSPO (Madishetti *et al*., 2010). The polymers were dissolved in chloroform and methanol along with plasticizer (Table 2). Then, the solution was poured into a glass Petri dish containing glycerin. The solvent was allowed to evaporate under room temperature for 24 h. The polymers (total weight: 500 mg) and drug (20 mg) were weighed in requisite ratios and dissolved in 10 mL of chloroform and methanol and PEG 400. After vortexing, the solution was poured on glycerin placed in a glass Petri dish and dried at room temperature for 24 h.

Dose Calculations

Width of the plate = 5 cm, length of the plate = 12 cm, No. of 2.5 × 2.5 cm^2 wafers present whole plate = 12, each wafer contains 10 mg of drug, 12 no. of wafers contains mg of drug= 20×12 = 240 mg, the amount of drug added in each plate was approximately equal to 240 mg.

Evaluation Parameters

The prepared transdermal patches were evaluated for the following parameters (Table 3):

Microscopic Evaluation

An optical microscope (Olympus-Cover-018) with a camera attachment (Minolta) was used to observe the shape of the prepared transdermal patch for all formulations.[11]

Table 4: *In vitro* drug release data for optimized formulation F2

Time (h)	Square root of time (h) 1/2	Log time	Cumulative* % drug release	Log cumulative % drug release	Cumulative Drug remaining	Log cumulative % Drug remaining
0.5	0.707	−0.301	24.45	1.388	75.55	1.878
1	1	0	36.65	1.564	63.35	1.802
2	1.414	0.301	53.32	1.727	46.68	1.669
4	2	0.602	68.85	1.838	31.15	1.493
6	2.449	0.778	76.65	1.885	23.35	1.368
8	2.828	0.903	89.98	1.954	10.02	1.001
10	3.162	1	94.45	1.975	5.55	0.744
12	3.464	1.079	99.15	1.996	0.85	−0.071

Table 5: Regression analysis data of nitrendipine transdermal patches

Batch	Zero order	First order
	r^2	
F2	0.91	0.921

Thickness

The thickness of the patch was measured by Vernier calipers. The thickness of patches was measured at three different places and an average of three readings was taken with standard deviation (Tanwar *et al*., 2007).[12]

Folding Endurance

This was determined by repeatedly folding one film at the same place until it had broken. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance (Shivaraj *et al*., 2010).[13]

Tensile Strength

Cut the patch at the center having 2 cm length and 2 cm breadth. Patch was hanged on the top and lower side of the instrument, then start the switch, and note the reading on the screen. The thickness and breadth of strips were noted at three sites and the average value was taken for calculation. The tensile strength was calculated by dividing applied force by cross-sectional area (Alka *et al*., 2012).[14]

Percentage of Moisture Content

The prepared patches were weighed individually and kept in desiccators containing activated silica at room temperature for 24 h (Amish *et al*., 2012). Individual patches were weighed. The percentage of moisture content was calculated as the difference between the final and initial weight with respect to the initial weight.[15]

Percentage of Moisture Uptake

First, weighed the patches and then kept in a desiccator at room temperature for 24 h and then its exposed to 84% RH (A saturated solution of potassium chloride) in a desiccator. The % of moisture uptake was calculated by the difference between the final and initial weight with respect to the initial weight (Kriplani *et al*., 2018).[16]

Drug Content Analysis

The patches ($n = 3$) of a specified area (6.16 cm^2) were taken into a 10 mL volumetric flask and dissolved in methanol (10 mL) with the help of shaker. After the vortex, the solution was filtered and prepared subsequent dilutions and analyzed by UV spectrophotometer at 222 nm (Teja *et al*., 2012).[17]

In Vitro Skin Permeation Study

The *in vitro* skin permeation study was done using a Franz diffusion cell (receptor compartment capacity: 80 mL: surface area: 3.14 cm^2. The egg membrane was separated and used for *in vitro* study (Table 4). The receiver compartment was filled with 40 mL of phosphate buffer, pH = 7.4. The transdermal patch was firmly pressed onto the center of the egg membrane and then the membrane

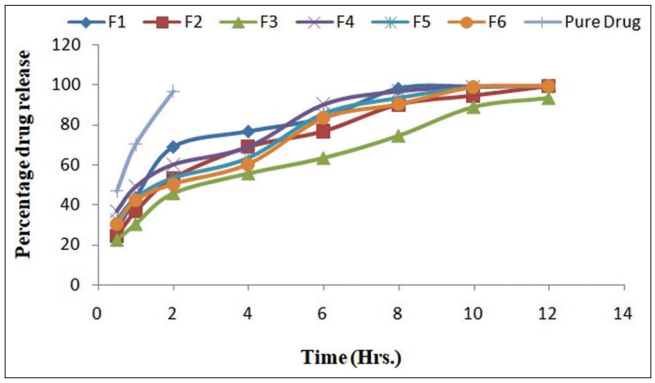

Figure 1: Percentage of drug release of nitrendipine transdermal patches

was mounted on the donor compartment (Vidyavati and Jithan, 2010). The donor compartment was then placed in a position such that the surface of the membrane just touches the receptor fluid surface. The whole assembly was kept on a magnetic stirrer with suitable rpm throughout the experiment using magnetic beads. The temperature of the receptor compartment was maintained at 37 ± 0.5°C.[18,19]

RESULTS AND DISCUSSION

In total, six formulations of transdermal patches were prepared and they were evaluated for various parameters. The thickness of the patch ranged from 89 ± 2 to 98 ± 6 µm. The folding endurance was observed to be extended from 178 ± 5 to 225 ± 7. The concentration of polymers also affects folding durability, which can result in outstanding fold qualities. The purpose of plasticizers in transdermal patches is to enhance the film's look and film-forming capabilities. The PEG 6000 in patches provides more flexibility at higher plasticizer concentrations. The % moisture content varied from 5.12 ± 0.22 to 5.69 ± 0.32% while the moisture uptake ranged from 3.12 ± 0.32 to 3.96 ± 0.23%.

Studies on the moisture content and moisture uptake of the patches showed a direct relationship between the concentration of hydrophilic polymer and the patches' increased moisture content and moisture uptake. The produced formulations had a low moisture content, which may have contributed to their stability and decreased brittleness after extended storage. In addition, the formulations' low moisture uptake may have reduced their bulkiness and shielded them from microbial contamination. In addition, the tensile strength was estimated as 0.45 ± 0.03 to 0.58 ± 0.03 kg/cm^2. The % drug content was found to be maximum for F2 formulation which is about 99.12 ± 0.23% and lowest in the case of F1 formulation which is about 96.65 ± 0.15%. The *in vitro* % drug release was noticed to be 99.45% in F1 and F6 formulations (Figure 1). Although the % drug release is better for F1 and F6, the F2 formulation is considered to be more superior and ideal by comparing between above-mentioned parameters.

The findings showed that as HPMC concentration rises, so does the medication release from the patches. In a 12-h period, the total percentage of drug release was recorded. It was discovered that when the hydrophilic polymer concentration in the polymer matrix increased, so did the drug release. This is because the creation of gelatinous holes is caused by the dissolution of a water-soluble component of the polymer matrix. When such pores are formulated, the mean diffusion path length of the drug molecules that are released into the diffusion medium decreases, increasing the release rate.

Further, the regression analysis of nitrendipine transdermal patches was carried out. Mainly the zero-order and first-order kinetics were in focus (Table 5). The zero-order kinetic model is a mathematical representation used to analyze drug release kinetics. It is characterized by a linear relationship between time and drug release, with a constant release rate. In this analysis, Batch F2 has an r^2 value of 0.910 for the zero-order model. The first-order kinetic model is another mathematical model used to describe drug release kinetics. It assumes that the drug release rate is directly proportional to the amount of drug remaining to be released. Batch F2 has an r^2 value of 0.921 for the first-order model. Thus, it can be clearly seen that the transdermal patch follows the first-order release kinetics.

CONCLUSION

The preparation technique for the transdermal nitrendipine patches used in this study is

straightforward. Excellent physicochemical qualities were also demonstrated by every formulation in terms of thickness, weight fluctuation, drug content, flatness, folding durability, moisture content, and moisture uptake. Still, the F2 formulation was considered as best. The *in vitro* release results demonstrated that the kinds and concentrations of polymers had an impact on the drug release from the patch formulation. Drug penetration *in vitro* has been examined in relation to the impact of penetration enhancers such as methanol and chloroform. These investigations showed that medication permeability increased with penetration enhancer concentration. The results of this study showed that putting nitrendipine topically in the form of a transdermal patch can alleviate the issues associated with its oral administration, such as limited absorption due to dissolution rate and gastrointestinal side effects so quite helpful in the treatment of patients with hypertension.

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