

FORMULATION AND EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM FOR LERCANIDIPINE HYDROCHLORIDE

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Abstract: Lercanidipine HCl is poorly absorbed after oral administration with peak plasma concentrations in 1 to 3 hours after a dose. Bioavailability is about 44% and extensively metabolized in liver. The half life is about 4.6 hours. Lercanidipine HCl due to its low therapeutic dose (2.5-20mg) and substantial biotransformation in liver becomes it ideal candidate for design and development of transdermal therapeutic system. Lercanidipine hydrochloride patches were prepared by using different concentration of Eudragit RS100, Hydroxypropyl methyl cellulose and ethyl cellulose using solvent casting techniques on a mercury substrate and the effect of polymer on the various physicochemical characteristics and in vitro drug release studies, ex vivo skin permeation studies. Formulations were prepared by taking 20 mg (Lercanidipine HCl), 10% w/w of propylene glycol and 10% w/w of dibutyl phthalate in ethanol. The formulations exhibited uniform thickness, weight and good uniformity in drug content. The maximum drug releases in 24 hrs for formulations were depending on the hydrophobicity of the polymer. On the basis of in vitro drug release and ex vivo skin permeation studies, Formulation containing (Eudragit RS100 and Hydroxypropyl methyl cellulose) was showed sustained and extended drug release over a period of 24 hrs. In Vitro and Ex vivo permeation of Lercanidipine HCl shows that patches of ERS 100: HPMC are suitable compared to ERS 100: EC patches. The results of the study show that Lercanidipine HCl could be administered transdermally over a period of 24 h. through the matrix type TDDS for effective control of hypertension.

Keywords: Transdermal, lercanidipine hydrochloride, Eudragit RS 100, HPMC, EC, In vitro drug release, Ex vivo permeation.

Introduction

Delivery of drugs into systemic circulation via skin has generated a lot of interest during the last decade as transdermal drug delivery systems (TDDS) offer many advantages over the conventional dosage forms and oral controlled release delivery systems notably avoidance of hepatic first pass metabolism, decrease in frequency of administration, reduction in gastrointestinal side effects and improves patient compliance¹. Matrix based transdermal formulations have been developed for a number of drugs such as metoprolol², nitrendipine³, ephedrine⁴, ketoprofen⁵, propranolol⁶, labetalol hydrochloride⁷, and triprolidine⁸.

Lercanidipine hydrochloride is a potent antihypertensive and antianginal drug. Lercanidipine HCl is poorly absorbed after oral administration with peak plasma concentrations in 1 to 3 hours after a dose. Bioavailability is about 44% and extensively metabolized in liver. Lercanidipine HCl is metabolized primarily via the cytochrome P450 isoenzyme 3A4. The half life of lercanidipine is about 4.6 hours. Lercanidipine HCl due to its low therapeutic dose (2.5-20mg) and substantial biotransformation in liver becomes it ideal candidate for design and development of transdermal therapeutic system. Lercanidipine HCl in transdermal formulations provides sustained blood levels over a prolonged period, which is required for control of hypertension⁹.

In spite of several advantages offered by transdermal route, only a few drug molecules are administered transdermally because the formidable barrier nature of stratum corneum. Two major approaches to increase transdermal permeation rate include physical techniques (iontophoresis, electroporation, sonophoresis, and microneedles) and use of chemical penetration enhancers (PE) such as solvents, surfactants, fatty acids, and terpenes¹⁰. The objective of this study was to formulate transdermal patches of Lercanidipine HCl and to evaluate the effect of polymer on the drug release.

Materials and Methods

Materials

Lercanidipine HCl, from Aurobindo Pharmaceuticals (Hyderabad, India). Eudragit RS100, hydroxypropyl methyl cellulose (HPMC), ethyl cellulose (EC), Propylene glycol (PG), Dibutyl phthalate obtained from Vikram Thermo (India) Ltd. All the chemicals used were of analytical grade.

Preparation of TDDS

Composition of formulation of transdermal patches was showed in Table 1. The polymeric solution (10% w/v) was prepared by dissolving Eudragit RS, (Eudragit RS100: Hydroxypropyl methyl cellulose) and (Eudragit RS100: Ethyl cellulose) in different ratios, along with drug, DBP and PG in ethanol. The solution was poured into a glass ring placed on the surface of liquid mercury kept in a Petri dish. The patches were kept at room temperature to evaporate the solvent over night. After complete drying of the patch aluminum foil was used as backing film. The patches were cut to desire size and stored in desiccator untill use.

Physicochemical Evaluation

Thickness and Weight Variation¹¹.

The thickness of the patches was assessed at six different points using screw gauze and the average weight of three patches was calculated.

Folding Endurance¹².

It was determined by repeatedly folding a small strip of films at the same place till it broke. The number of times, the films could be folded at the same place without breaking gave the value of folding endurance.

Drug Content Determination¹³.

The patch (1 cm²) was cut and added to a beaker containing 100 ml of phosphate buffered pH 7.4. The medium was stirred (500 rpm) with teflon coated magnetic bead for 5 hours. The contents were filtered using whatman filter paper and the filtrate was analyzed by U.V.spectrophotometer (Elico, SL-164, Hyderabad, India) at 240 nm for the drug content against the blank solution.

Percent Moisture Absorption¹⁴.

The films were placed in dessicator containing saturated solution of aluminum chloride, keeping the humidity inside the dessicator at 79.5% RH. After 3 days the films were taken and weighed the percentage moisture absorption of three films were determined.

Percent moisture absorption =

$$\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percent Moisture Loss¹⁵.

This test was also carried to check the integrity of films at dry condition. Three films of 5 square centimeter area was cut out and weighed accurately and kept in a dessicator containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. Average percentage moisture losses of three films were determined.

Percent moisture loss =

$$\frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

In vitro drug release studies¹⁶.

The in vitro release was carried out with the semi permeable membrane using open ended cylinder. The cylinder consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The temperature was maintained at $37 \pm 0.5^\circ \text{C}$ and receptor compartment was provided with sampling port. The diffusion medium used was phosphate buffer (pH 7.4). The drug containing patch with a support of backing membrane was kept in the donor compartment and it was separated from the receptor compartment by semipermeable membrane. The semipermeable membrane was previously soaked for 24 hours in phosphate buffer (pH 7.4). The receptor compartment containing 300ml phosphate buffer (pH 7.4) in a beaker was maintained at $37 \pm 0.5^\circ \text{C}$ and stirred at 50 rpm with magnetic beads operated by magnetic stirrer. A sample of 1 ml was withdraw at predetermined time intervals and replaced with fresh buffer. The concentration of drug was determined by spectrophotometrically at 240nm.

Preparation of Skin

Ex vivo Skin Permeation Studies¹⁷.

The in vitro skin permeation studies were carried out using dorsal section of full thickness skin from albino rats (weighing between 200-250 g) whose hair had

been removed. The transdermal patches were firmly pressed on the centre of the rat skin. Once adhesion to the skin surface had been confirmed, the skin was quickly mounted on the diffusion tube which acted as the donor compartment. 100 ml of phosphate buffer of pH 7.4 taken in a beaker, which acted as the receptor compartment to maintain the sink condition. The donor compartment was kept in contact with the receptor compartment and the receptor compartment was stirred magnetically during the study. After every 1 hrs sample (1ml) was withdrawn at predetermined time intervals and replaced with fresh buffer. The concentration of drug was determined by U.V. spectrophotometrically at 240 nm.

Results and Discussion

The physicochemical characteristics of prepared patches are showed Table 2. The weights are ranged from 19.4 ± 2.66 to 22.3 ± 1.55 mg. Thickness ranged from $125 \pm 3 \mu$ to $137 \pm 4 \mu$. The weights are found to be high with films prepared with higher proportions of HPMC. As the proportion of HPMC was decreased, the thickness was also decreased. Good uniformity in drug content was observed and it ranged from 96.57 ± 0.16 mg to 98.49 ± 0.35 in all the formulation.

The folding endurance was found to be between 217 ± 4.43 to 250 ± 2.90 . The moisture loss in the range of 5.10 ± 0.18 to 12.42 ± 0.20 and moisture absorption in the range of 4.64 ± 0.02 to 10.33 ± 0.04 found to be satisfactory.

In vitro release studies

ERS100 are copolymers of acrylic and methacrylic acid esters with a low content (2.5-5%) of quaternary ammonium groups. The ammonium groups are responsible for the permeability and swelling of these water-insoluble films. The lower proportion of ammonium groups in Eudragit RS100 is responsible for controlling the release of drug. A suitable proportion of RS100 may be used to achieve prolonged release of the drug. Along with the Eudragit RS100 the other polymer like HPMC and EC are used. Release rates were increased when the concentration of HPMC increased in the formulations. This is because as the proportion of this polymer in the matrix increased, there was an increase in the amount of water uptake and hydration of the polymeric matrix and thus more drugs was released. The EC was used to retard the release of the drug from the matrix due to the more hydrophobic nature, therefore the prolonged drug release was obtained. The formulation containing Eudragit RS100 and HPMC showed 96.23 % drug release over 24 hrs due to hydrophobic and hydrophilic nature of the polymers. Whereas the Eudragit RS100 alone showed 76.37 % drug release in 24 hrs and when Eudragit RS100 and EC showed 63.47% drug

release in 24 hrs due to hydrophobic nature of both the polymer. The results of in vitro drug release studies from transdermal patches were showed in Fig 1.

Ex vivo skin permeation studies

The results of ex vivo permeation of Lercanidipine HCl from patches are shown in Fig 2. The order of drug permeation from different formulations was increased in the following order: F-2>F-3>F-1>F-4>F-5. The results corroborated that higher the drug release from the formulation, higher was the rate and extent of drug permeation. Percent drug release from the formulation F-2 was higher than other leading to conclusion that ERS 100 and HPMC combination is better than ERS 100 and EC as the polymeric precursor for the Lercanidipine HCl transdermal patches. As the concentration of hydrophilic polymer was increased, the amount of drug permeated was increased. This may be a result of the initial rapid dissolution of the hydrophilic polymers when the patch is in contact with the hydrated skin, which results in accumulation of high amounts of drug on the skin surface and thus leads to the saturation of the skin with drug molecules at all times. Drug release rate from films containing higher proportions of lipophilic polymer ERS 100 and EC may be contributed to the relatively hydrophobic nature of polymer which has less affinity for water. This results in decrease in the thermodynamic activity of the drug in the film and decreased drug permeation.

Comparison between all the formulations revealed that extent of drug release was higher in case of (polymers ERS 100 and HPMC) than (polymers ERS 100 and EC). The maximum drug permeation from formulation F2 might be due to higher permeability characteristics of HPMC in comparison to EC. Any vehicle can have three models of penetration enhancement that is by changing thermodynamic activity or by improving skin/ vehicle partition coefficient or by altering the barrier property of stratum corneum.

Propylene glycol (PG) action as a sorption promoter has been explained in the literature on the basis of its co solvency effect. Where thermodynamic activity is considered as main driving force and also by carrier mechanism, in which PG partition into the skin and thereby promotes the movement of the drug into and through the skin.

Conclusions

In Vitro and Ex vivo permeation of Lercanidipine HCl shows that patches of ERS 100: HPMC are suitable compared to ERS 100: EC patches. The results of the study show that Lercanidipine HCl could be administered transdermally over a period of 24 h. through the matrix type TDDS for effective control of hypertension.

Table 1. Composition of Lercanidipine HCl Transdermal Delivery Systems

S.No.	Formulation Code	Drug (mg)	Polymer		
			ERS 100	ERS100:HPMC	ERS 100: EC
1	F- 1	20	10	-	-
2	F - 2	20	-	3:7	-
3	F - 3	20	-	7:3	-
4	F- 4	20	-	-	3:7
5	F- 5	20	-	-	7:3

All the formulations carried 10 % w/w propylene glycol as penetration enhancer

All the formulations carried 10 % w/w dibutyl phthalate as plasticizer.

Table 2. Physicochemical Characteristics of Prepared Films

S.No.	Formulation code	Mean Thickness (μ)	Moisture Loss (%)	Moisture Absorption (%)	Drug Content (%)	Folding Endurance	Weight (mg)
1	F- 1	132 \pm 3	6.97 \pm 0.06	7.40 \pm 0.05	97.20 \pm 0.34	217 \pm 4.43	20.3 \pm 2.58
2	F - 2	137 \pm 4	10.15 \pm 0.45	9.36 \pm 0.12	98.08 \pm 0.12	233 \pm 2.36	22.3 \pm 1.55
3	F - 3	125 \pm 3	12.42 \pm 0.20	10.33 \pm 0.04	98.49 \pm 0.35	244 \pm 1.46	19.43 \pm 2.50
4	F- 4	132 \pm 3	5.10 \pm 0.18	4.64 \pm 0.02	96.43 \pm 0.24	250 \pm 2.90	21.3 \pm 2.21
5	F- 5	131 \pm 3	8.18 \pm 0.02	7.25 \pm 0.03	96.57 \pm 0.16	225 \pm 3.55	21.2 \pm 2.36

Mean \pm S.D (n=3)

Table 3. In vitro drug release and skin permeation of lercanidipine hydrochloride transdermal patches.

Formulation Code	% of drug released in 24 hrs	% of drug permeated in 24 hrs
F- 1	76.37	65.87
F - 2	96.23	85.25
F - 3	87.52	77.32
F- 4	66.71	55.45
F- 5	63.47	47.65

Fig. 1 Comparison of In vitro release profiles of lercanidipine hydrochloride Transdermal patches

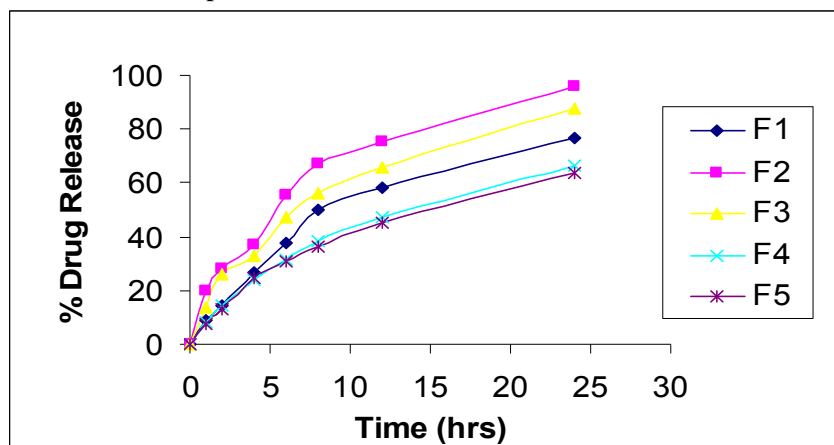
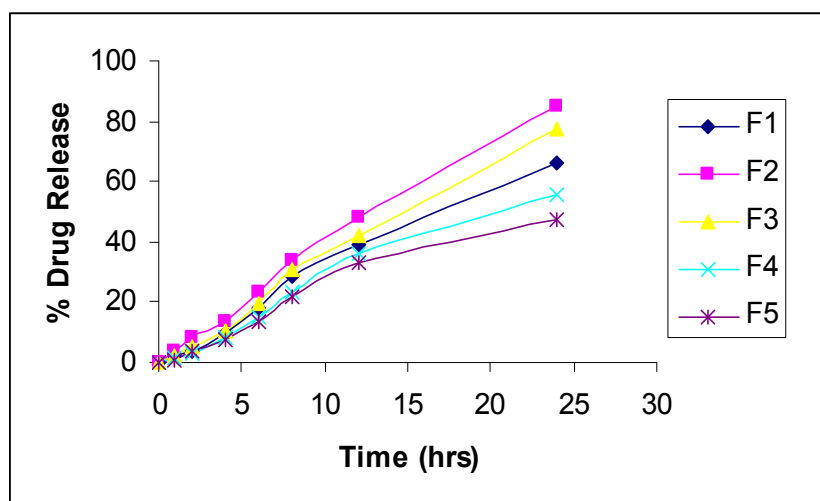


Fig. 2 Ex vivo permeation profiles of lercanidipine hydrochloride from Transdermal patches



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