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Research Article

FEASIBILITY OF LERCANIDIPINE HCL FOR TDDS: PERMEATION KINETIC STUDY IN PRESENCE OF VARIOUS PENETRATION ENHANCERS

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ABSTRACT

Delivery of drugs through the skin has invited great attention since past decades. Currently, few number of transdermal drug delivery systems are available commercially. Because of complicated bioarchitecture and composition of the stratum corneum have severely limited the number of molecules that can be delivered passively across the skin. Among the different methods employed to increase the skin permeation of drugs, penetration enhancers are one of the most convenient method and exhibited relatively strong effects. In this study, lercanidipine hydrochloride a widely used potent antihypertensive and antiangianl drug which undergoes extensive first pass metabolism in liver and exhibits low bioavailability, about 44%, has chosen. The study was conducted with the aim to check the feasibility of this drug for transdermal drug delivery system. Initially, passive diffusion of drug was carried out and later, the diffusion studies of drug were conducted in presence of various penetration enhancers such as dimethyl sulfoxide, eugenol, citral, sodium lauryl sulphate and isopropyl myristate through modified franz diffusion cell. Also, flux and permeation coefficient and enhancement ratios of drug and penetration enhancers were calculated and the satisfactory results were exhibited.

Keywords: Lercanidipine hydrochloride, Stratum corneum, Permeation kinetics, Penetration enhancers, Flux, Permeation coefficient.

INTRODUCTION

Among all organs, skin is the most expansive organ of the human body. In recent years, it has been widely used as a major pathway for pharmaceutical drugs with local action, and it is now popularly identified for other drugs with systemic action [1]. Currently, several transdermal drug delivery systems (TDDS) containing drugs such as clonidine, estradiol, fentanyl, nicotine, nitroglycerin, oxybutynin and scopoloamine are available in the United States [2].

Transdermal Drug Delivery (TDD) presents a potential advantageous mode of drug delivery in that it eliminates first pass metabolism and provides a sustained release of drugs for a prolonged duration of time. However, very low skin permeability of foreign molecules across it, still poses severe limitations in utilizing TDD [3]. Because of diverse complicated bioarchitecture and composition of the stratum corneum have severely limited the number of molecules that can be delivered passively across the skin [4]. Several methods such as penetration enhancers, prodrugs, superfluous vehicles, iontophoresis, phonophoresis and thermophoresis have been employed to increase the skin permeation of drugs. Among all, penetration enhancers are one of the most convenient method and exhibited relatively strong effects [5].

In this study, lercanidipine hydrochloride (lercanidipine HCl), a potent antihypertensive and antianginal drug, is selected as a model drug for checking the suitable drug candidate for transdermal drug delivery system (TDDS). It shows poor absorption after oral administration with peak plasma concentrations in 1.5 to 3 hours after a dose. It's plasma half-life is about 2-5 hours and undergoes extensive saturable first pass metabolism in liver and exhibits low bioavailability, about 44%, made it an ideal drug candidate for TDDS studies [6, 7]. The target of this study was to study the feasibility of lercanidipine HCl for formulation of transdermal drug delivery.

MATERIALS AND METHODS

Lercanidipine hydrochloride IP was gifted by Glenmark Pharmaceuticals, Gujarat, India. Dimethyl sulfoxide (DMSO), Eugenol, Citral, Sodium lauryl sulphate (SLS) and Isopropyl myristate (IPM) was procured from S.D. Fine Chemicals Ltd., Mumbai, India.

Identification of drug by analytical tools

IR (Infra-red) spectroscopy analysis

FT-IR spectroscopy (Perkin-Elmer FTIR spectrophotometer, Model 1600, Japan) is employed as analytical tool to check the procured drug as lercanidipine hydrochloride, using KBr disc method. FTIR spectra were scanned and recorded for drug between 400 and 4000 cm^{-1}.

DSC (Differential Scanning Colorimetry) analysis

One more drug identification study was carried out using DSC analysis (Mettler-Toledo Star System, IISc, Bangalore, India). DSC thermogram of drug was obtained by hermetically sealing a sample of drug in flat-bottomed aluminum pans at a ratio of 1:1 was scanned over a thermal range of 50-250ºC at a rate of 10°C/min using alumina as a reference standard, in a cool environment generated through liquid nitrogen.

Effect of pH on drug solubility

The solubility of lercanidipine HCl was determined in phosphate buffer solutions of various pHs 4.0, 5.0, 6.2, 7.4, 8.0 and 9.0. In this method, to the 10 ml phosphate buffer solutions of each pH in a conical flask excess drug was added and the samples were kept for agitation on a mechanical shaker for 24 h at 37±0.2^0 C. The pH of the samples was checked and adjusted the pH with 0.1 M perchloric acid whenever necessary. After the specified time, the suspensions were filtered using 0.45 µ whatman filter paper. The concentration of lercanidipine HCl in filtrate was assayed spectrophotometrically by measuring at 236 nm [8].

Partition coefficient of drug in n - octanol/water system

Determination of partition coefficient of drug was carried out using equal volume of n-octanol and aqueous solution in a separating funnel. In case of water- soluble drugs, a drug solution with a concentration 25 µg/ml is needed to be prepared in distilled water. If in case of water insoluble drugs (eg., Lercanidipine Hcl), a drug solution of 25 µg/ml is needed to be prepared in n-octanol [9]. 25 ml of this solution was taken in separating funnel and shaken with equal volume of 1-octanol/water system at an interval of 1 h for a period of 24 h and allowed to stand for 1 h. The mixture was then vortexed at 2000 rpm for 10 minutes and concentration of drug extracted in each phase was assayed spectrophotometrically by measuring

absorbance at 236 nm. The partition coefficient (Kp) was calculated from the below equation.

$$Kp = \frac{\text{concentration of drug in organic phase}}{\text{concentration of drug in aqueous phase}}$$

***Ex-vivo* permeation kinetic studies**

Skin preparation

The fresh full thickness (75-80µm) porcine skin was obtained from local slaughter house. The hairs of skin was carefully trimmed to short using a sharp scissor and was stored in water thermostated at 60°C for a period of 5 min to separate the epidermis and dermal joint. The isolated epidermis (25±5 µm) was rapidly rinsed with hexane to remove the lipid content, rinse with water and then either used or stored at frozen conditions (for not more than 78 h) in an aluminum foil for further use [10].

Permeation kinetic studies

The permeation kinetic studies of the drug were conducted using a standardized glass *in-vitro* modified Franz diffusion cell (25 ml capacity), consisting of top (donor) and bottom (receptor) compartments. The diameter of donor compartment provided 3.60 cm^2 effective constant area for diffusion studies with saturated solution of drug and drug with penetration enhancers.

The receptor compartment was introduced with phosphate buffer (pH 7.4) as the diffusion medium and a small bar magnet was placed to stir the medium for uniform drug distribution. The diffusion cells were water jacketed, and maintained at a constant temperature of 37±1°C by thermostatic arrangement. Excised epidermal membrane was clamped between the donor and receptor compartment of the diffusion cell. The entire assembly was placed on the ready to operate thermostatic controlled magnetic stirrer (Remi Motors Pvt Ltd, Vasai, India). Initally, the studies was done with 5 ml saturated solution of the drug containing a portion of suspended excess drug only. Later on, studies were continued with a suspension of drug and permeation enhancers. An aliquot of 5 ml was withdrawn at predetermined intervals for duration of 12 hours. The drug concentration in the aliquots was estimated spectrophotometrically (Shimadzu UV-1800, Japan) at 236 nm.

As said in above paragraph, the chemical penetration enhancers selected for the study were DMSO, Eugenol, Citral, SLS and IPM. The donor compartment was presented with a suspension of drug and 5% v/v concentration of different enhancers. All other experimental conditions and analytical tools followed were similar to those reported in permeability study part.

RESULTS AND DISCUSSION

IR (Infra-red) spectroscopy analysis

When we observe the Fig. 1 of FTIR spectra of drug, exhibited the peaks at 3078.8 cm^{-1} for C-H aromatic stretching, 1347.03 cm^{-1} for $-NO_2$, 1672.95 cm^{-1} for >C=0 stretching vibrations and 1486.85 cm^{-1} for $-CH_3$ bending vibration. When the peaks are compared with the literature, it was cleared that all peaks are coincidence [10].

DSC analysis

On observation of Fig. 2 of the DSC thermogram of drug displayed the characteristic peak at 196.68°C corresponding to its melting point as presented in literature [11].

On the basis of results obtained from the above two analytical tools, it can clearly indicates that the obtained drug was lercanidipine hydrochloride.

Effect of pH on drug solubility

The values for solubility of drug in isotonic phosphate buffer solutions of various pHs were found to be 0.286, 0.547, 0.876, 1.243, 1.546, and 1.786 mg/ml in 4.0, 5.0, 6.2, 7.4, 8.0 and 9.0 pH buffers respectively. By observing results it can clearly indicated that as the pH of the buffer increased, the solubility of drug was also increased. Fig. 3 represents the effect of pH on the solubility of drug in various pHs.

Partition coefficient of drug in n - octanol/water system

n - octanol and *in - vitro* fluid (in this case, phosphate buffer of various pHs) are considered as the standard solvent system for determining the drug partition coefficient between the skin and *in - vitro* fluid. The values for partition coefficient of drug in n - octanol/water system was found to be 6.75, 6.79, 6.81, 6.84, 6.85 and 6.88 in varied range of phosphate buffers 4.0, 5.0, 6.2, 7.4, 8.0 and 9.0 pHs respectively. The obtained results indicated that the drug possess enough lipophlic property which meets the requirements of formulating it into a TDDS.

***Ex-vivo* permeation kinetic studies**

Steady state permeation kinetic studies were performed using a standardized glass *in-vitro* modified Franz diffusion cell and porcine skin was used as a barrier membrane in triplicate in passive diffusion fashion. The results of percentage cumulative release for drug and along with various enhancers are displayed in Table 1 and Fig. 4. The values for permeability coefficient and flux of drug were found to be 0.492 cm/min and 1.23 µg /cm^2/min respectively.

The enhancement ratios of drug with various penetration enhancers with constant concentration about 5% was studied using *in-vitro* modified Franz diffusion cell through porcine skin. All values related to permeability coefficient, flux and enhancement ratios of drug are depicted in Table 2. The permeability coefficient, flux and enhancement ratios of drug with different penetration enhancers found to be in increasing order as follows: IPM > SLS > Citral > Eugenol > DMSO. Fig. 5 represents the bar graph displays the enhancement ratios of the drug and penetration enhancers.

Terpenes such as eugenol and citral exhibited the mechanism of enhancement of diffusivity of the drug through the stratum corneum either by disruption of the intercellular lipid barrier or by opening polar channels in the stratum corneum through increasing electrical conductivity of tissues [12] or by increasing the thermodynamic activity of drug [13]. The long chain fatty acid esters such as IPM might have shown enhancement effect by partitioning at high concentrations to the skin, which makes it to increase in the diffusion rate of drug [14]. The enhancement ability of anionic surfactants such as SLS may be through interaction with the stratum corneum by increasing local water concentration with successive swelling and expansion of the thickness of the tissue [15]. Among all, the DMSO exhibited highest enhancement ratio. This may be due to either due to extraction of skin lipids or denaturation of stratum corneum proteins or formation of hydrogen-bonded complexes with stratum corneum lipids and the distortion [16].

Equations for calculating permeability coefficient (P), flux (J), enhancement ratio as follows: [8]

Permeability coefficient (P) is the velocity of drug passage through the membrane in µg/cm^2/min. It was calculated from the slope of the graph of percentage of drug transported versus time as

$P = \text{Slope} \times Vd/S$

Where Vd = Volume of donor solution; S = Surface area of tissue.

Flux (J) = Flux is defined as the amount of material flowing through a unit cross sectional barrier in unit time. It is calculated by using following eqation:

$Flux\ (J) = P \times CD$

Where CD = Concentration of donor solution; P = Permeability

Enhancement ratio: Enhancement ratio was used to evaluate the effect of permeation enhancer on diffusion and permeation of selected drug molecules. It is calculated by using below mentioned equation:

$$\text{Enahncement ratio} = \frac{\text{Permeability coefficient of drug with enhancer}}{\text{Permeability coefficient of drug alone}}$$

Table 1: Preformulation screening data of drug with different enhancers

Time (Minutes)	Drug (Lercanidipine HCl)	DMSO	Eugenol	Citral	SLS	IPM
10	1.33±0.21	2.36±0.43	3.14±0.23	2.52±0.24	2.12±0.02	1.71±0.43
20	1.66±0.01	3.96±0.54	4.58±0.87	3.42±0.86	2.60±1.23	1.90±0.71
30	2.18±0.34	4.50±0.89	5.88±0.32	3.92±0.72	3.1±1.70	2.36±0.31
60	2.48±0.65	4.50±0.13	6.66±0.45	4.94±0.65	3.46±0.89	3.01±0.92
120	2.91±0.02	5.50±0.55	7.38±0.54	5.90±0.11	4.86±0.23	6.44±0.45
240	3.91±0.12	8.08±0.12	8.20±0.21	8.16±0.82	6.58±0.78	9.82±0.63
360	4.38±0.25	9.10±0.64	10.12±0.34	9.64±0.52	8.06±0.39	13.26±0.09
480	5.24±0.23	10.58±0.77	21.86±0.87	11.04±0.44	9.54±0.68	17.42±0.33
720	6.00±0.71	25.02±0.27	34.02±0.23	17.90±0.38	11.28±0.99	22.42±0.72
1440	8.97±0.87	72.08±0.98	69.28±0.12	38.46±0.28	44.9±1.12	33.87±0.69

(n = 3)

Table 2: Data of Permeability Coefficient, flux and Enhancement Ratio of drug and drug with permeation enhancers

Name	Permeability coefficient (cm/min)	Average flux (µg/cm²/min)	Enhancement Ratio
Drug	0.492	1.23	1
DMSO	1.34	3.36	2.72
Eugenol	1.32	3.32	2.68
Citral	0.948	2.37	1.92
SLS	0.764	1.91	1.55
IPM	0.684	1.71	1.39

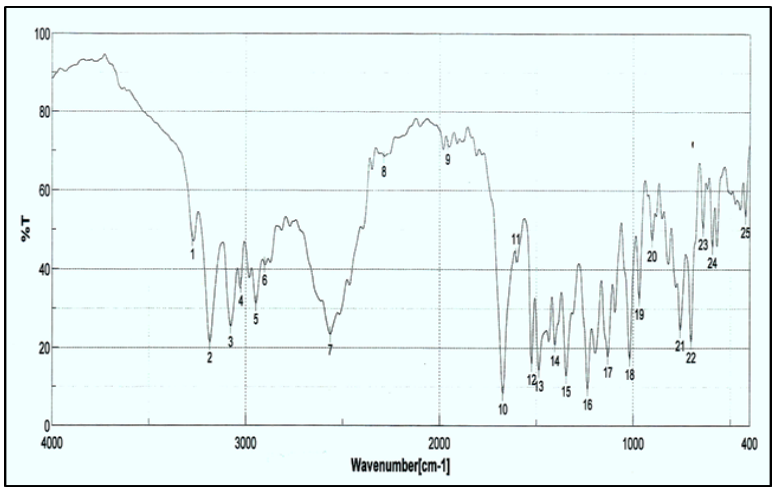

Fig. 1: FTIR spectra of Lercanidipine HCl

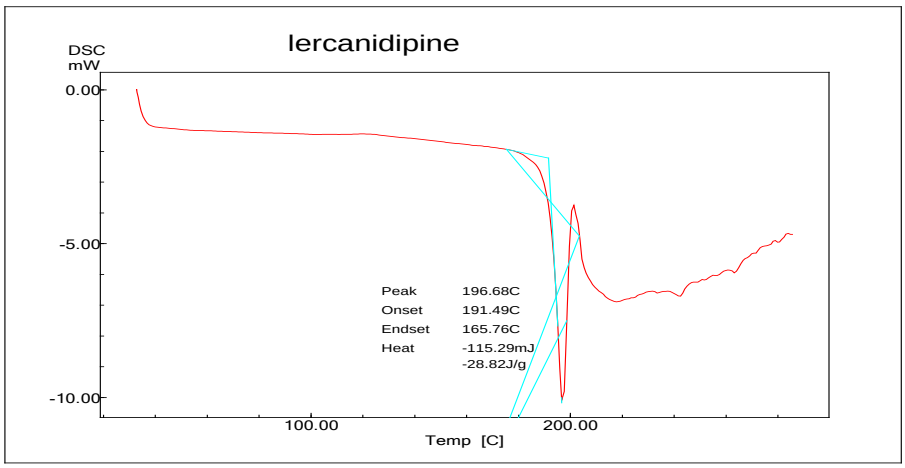

Fig. 2: DSC thermogram of Lercanidipine HCl

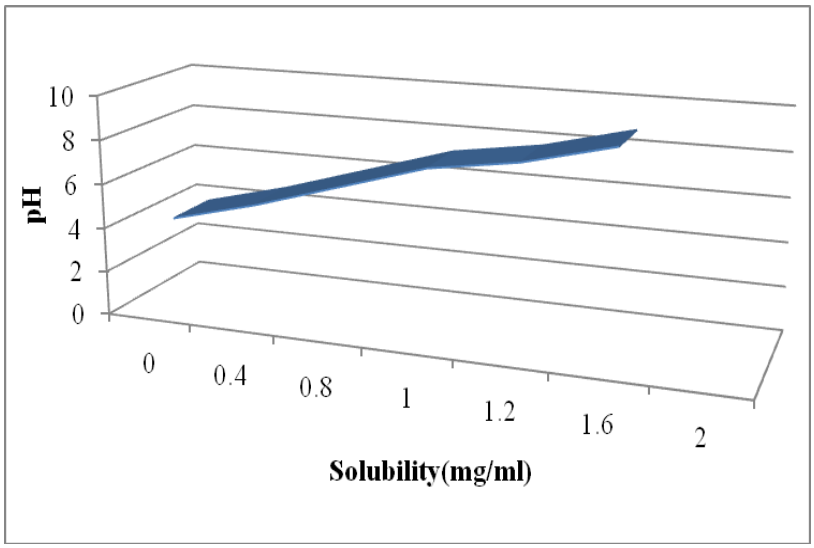

Fig. 3: Effect of pH on drug solubility

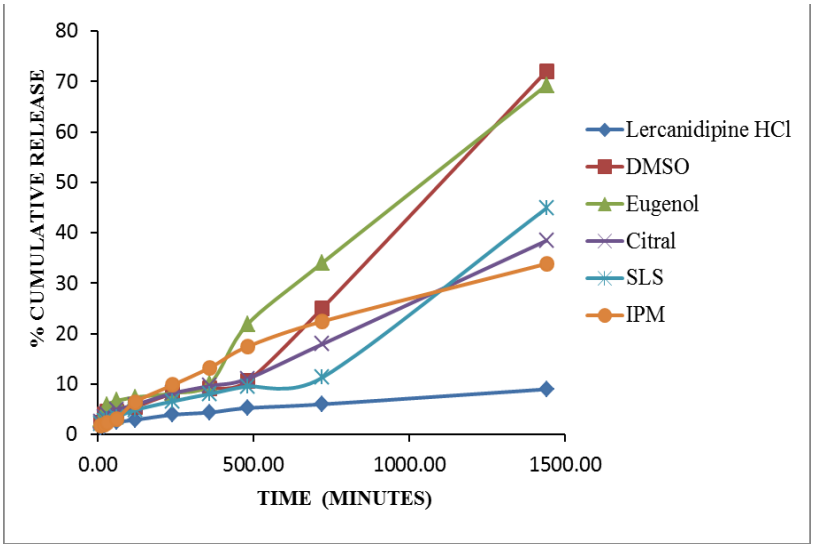

Fig. 4: Preformulation screening data of drug with various enhancers

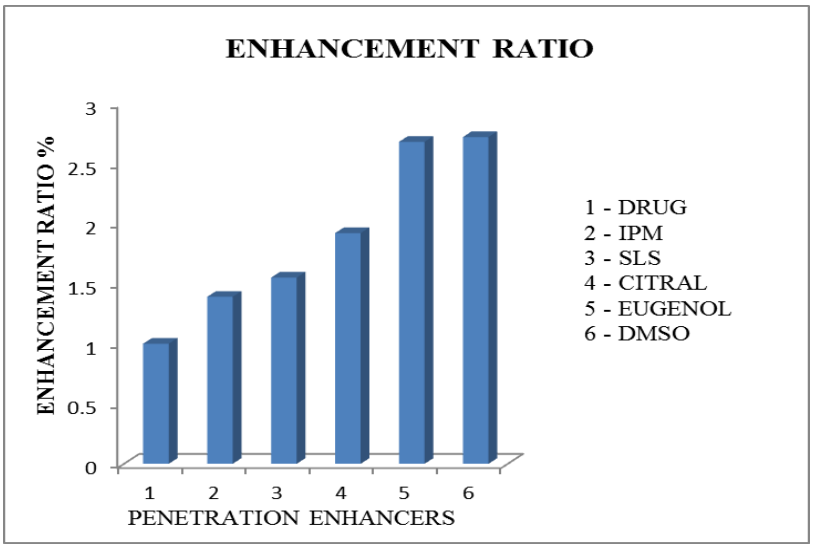

Fig. 5: Bar graph showing enhancement ratio of Lercanidipine Hcl with different penetration enhancers (n = 3)

CONCLUSION

In this study, we studied the feasibility of Lercanidipine hydrochloride, a potent antianginal and antihypertensive drug for formulation of transdermal drug delivery system. During *ex-vivo* permeation study, five different chemical penetration enhancers with 5% concentration were used. The satisfaction results say penetration of drug can be enhanced in presence of dimethyl sulfoxide penetration enhancer. From the study it can be concluded that the drug Lercanidipine hydrochloride is suitable for administration through transdermal drug delivery system.

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