Available online on 15.08.2023 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

Formulation development and characterization of Lecarnidipine hydrochloride niosomal transdermal patches

B. Padmaja[1]*, S. Shobha Rani[2]

[1] *Department of Pharmaceutics, Vaageswari Institute of Pharmaceutical Sciences, Karimnagar, 505481, Telangana, India*

[2] *Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad, 500085, Telangana, India*

Article Info:

Article History:

Received 19 May 2023
Reviewed 04 July 2023
Accepted 23 July 2023
Published 15 August 2023

Cite this article as:

Padmaja B, Shobha Rani S, Formulation development and characterization of Lecarnidipine hydrochloride niosomal transdermal patches, Journal of Drug Delivery and Therapeutics. 2023; 13(8):100-109

DOI: http://dx.doi.org/10.22270/jddt.v13i8.5942

*Address for Correspondence:

B. Padmaja, Department of Pharmaceutics, Vaageswari Institute of Pharmaceutical Sciences, Karimnagar-505481, Telangana-500085, INDIA

Abstract

The bioavailability of Lercanidipine Hydrochloride (LCP) is about 44% and half-life of the drug is about 4.6 hours. LCP due to its low therapeutic dose range of 2.5 to 20mg and substantial biotransformation in liver becomes it ideal molecule in development of transdermal therapeutic system. The primary objective of the present research work was to develop Niosomal transdermal patch (NP) of Lecarnidipine. The LCP nanoparticles were prepared by solvent evaporation method and the optimized Nanoparticles formulation has shown 225nm particle size with a polydispersity index (PDI) of 0.120. LCP patches were prepared by incorporating nanoparticles dispersion, using varying concentrations of polymers HPMC E5, HPMC 5cps, HPMC 15cps, Carbopol 734 and Sodium alginate using solvent casting techniques and further optimized by central composite design(CCD) the effect of polymer on the various physico-chemical characteristics and in-vitro drug release studies, ex-vivo skin permeation studies is studied. On the basis of in-vitro drug release and ex-vivo skin permeation studies, the formulation containing (HPMC 15cps and HPMC 5cps) has shown sustained and extended drug release over a period of 24 hrs.

Keywords: Lecarnidipine; Niosomes; Transdermal patch; Central composite Design, Controlled release; Bioavailability etc.

1. INTRODUCTION

Lecarnidipine Hydrochloride (LCP) is chemically known as 1, 4-Dihydro- 2,6-dimethyl -4-(3- nitrophenyl) -3,5-pyridine dicarboxylic acid 2- [(3,3-diphenyl propyl) methyl amino]-1,1-dimethylethylmethyl ester hydrochloride. LCP is a calcium channel blocker for the management of hypertension which belongs to biopharmaceutical classification system II and the oral bioavailability of the drug is 44% due to extensive first pass metabolism[1]. LCP is having shorter half-life and the dose range is low which is highly suitable for transdermal drug delivery.

Niosomes are non-ionic surfactant vesicles obtained by hydrating mixture of cholesterol and nonionic surfactants. It can be used as carriers of amphiphilic and lipophilic drug. In niosomes drug delivery system, the medication is encapsulated in a vesicle[2–4]. Niosomes are biodegradable, biocompatible non-immunogenic and exhibit flexibility in their structural characterization. The LCP niosomes were prepared by thin film hydration technique and the optimized niosomes were formulated into transdermal patch by using various polymers for controlled release of the drug[2,3,5,6].

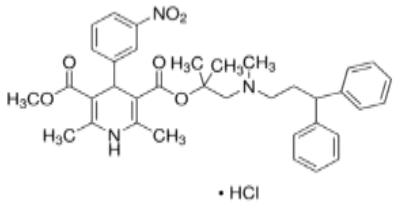

Figure 1: Molecular structure of Lecarnidipine Hydrochloride

Niosome have high entrapment efficiency, which is nearly 90% in the case of lipophilic drug. They protect the encapsulated drug from metabolic degradation. They act as depot, releasing their contents slowly and gradually. They can be used for both systemic as well as topical delivery of drugs. Thus, niosomes can increase the transdermal flux, prolong the release and improve the site specificity of bioactive molecules[5,6].

Niosomes penetrate the stratum corneum because of the transdermal hydration gradient normally existing in the skin, and then cross the epidermis, and enter the systemic circulation. The recent studies propose that the penetration and permeation of the vesicles across the skin are due to the combination of the two mechanisms. Depending on the nature of the active substance (lipophilic or hydrophilic) and the

composition of the niosomes, one of the two mechanisms prevails[5,6].

2. MATERIALS AND METHODS

2.1. Materials

Lecarnidipine obtained from Aurobindho Pharma Ltd, span 40, Span 60, Span 80, Tween 40, Tween 60, Tween 80, Cholesterol, soy lecithin, HPMC E5, HPMC 5cps, HPMC 15cps, Carbopol 734, sodium alginate, methanol, chloroform, PEG 200, glycerine, Labrasol ALF, Transcutol, Methanol (Merck), Orthophosphoric acid etc. All the chemicals were of analytical grade.

2.2. Methods

2.2.1. Determination of melting point of Lecarnidipine Hydrochloride by DSC

Differential Scanning Calorimetry (DSC) analysis of pure drug was carried out on Shimadzu Corporation Japan to check the purity of the drug. The drug Sample was placed in aluminium pans and were crimped followed by heating at rate of 5°C/min from 25 to 450°C temperature under a Nitrogen gas flow[7–9].

2.2.2. Analytical Method Development

Construction of Standard Graph of Lecarnidipine hydrochloride

Accurately weighed amount of 100 mg Lecarnidipine Hydrochloride was transferred into a 100ml volumetric flask. 20 mL of methanol was added to dissolve the drug and volume was made up to 100 mL with the same distilled water. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'. From this stock solution 10ml was taken and diluted to 100 mL with methanol which has given the solution having the concentration of 100µg/ml. Necessary dilutions were made by using this second solution to give the different concentrations of Lecarnidipine Hydrochloride (2 to 10 µg/ml) solution. Using a UV spectrophotometer, the absorbance of thus prepared solutions was scanned between 200-800nm in comparison to a blank.

2.2.3. Solubility of the Lecarnidipine Hydrochloride in various Excipients

The solubility of LCP was studied in various solvents. The excess amount of drug was added to 1ml of each excipient in cap vial bottle & cyclo-mixed immediately for 5min on cyclomixer (REMI CM 101). The concentration of drug in each excipient was quantified by UV- method[11].

2.2.4. Drug excipients compatibility studies

Fourier-transform infrared (FTIR) spectra of moisture-free powdered sample were obtained using a spectrophotometer by potassium bromide (KBr) pellet method. The scanning was done at 4000- 400cm-1, the resolution was cm-1. Similarly repeated for the drug and all the formulation excipients[12].

2.2.5. Preparation of Lecarnidipine Niosomes

The surfactants with highest solubility of LCP were choose for formulating Niosomes. Span 40, Span 60, Span 80, Tween 40, Tween 60 and Tween 80 were chosen for the study. The surfactants were placed in a round bottomed flask. The solvent system is then added to the mixture and the ingredients were dissolved in the solvent (Chloroform: methanol) by hand shaking. The flask was attached to a rotary evaporator and immersed in water bath maintained at 60˚C, rotated at 100rpm for 45min. Formation of thin film at the bottom was observed. The thin film is hydrated using 6.8pH buffer. The resultant solution was sonicated in Bath sonicator for 10mins. The niosomal dispersion formulations were shown in the Table-1 with various surfactants and their composition[2,5]. Design of experiments is used for optimization of niosomes and response surface graphs are shown in Fig-8.

Table 1: Composition of Lecarnidipine Niosomal Dispersion

Formulation code	Surfactant	Lercanidipine (mg)	Surfactant (mg)	Cholesterol (mg)	Soya Lecithin (mg)	Solvent (Chloroform: Methanol) (ml)	Buffer Solution (ml)
LN1	Span 40	200	100	100	50	2:1	4ml
LN2	Span 40	200	200	100	50	2:1	4ml
LN3	Span 60	200	100	100	50	2:1	4ml
LN4	Span 60	200	200	100	50	2:1	4ml
LN5	Span 80	200	200	100	50	2:1	4ml
LN6	Tween 40	200	200	100	50	2:1	4ml
LN7	Tween 60	200	200	100	50	2:1	4ml
LN8	Tween 80	200	200	100	50	2:1	4ml

2.2.6. Characterization of Niosomes

2.2.6.1. Particle size, PDI and Zeta potential

Determination of vesicle size, poly dispersity index and zeta potential the vesicle size, PDI and zeta potential of the prepared Niosomes were determined based on laser diffraction using the Malvern Master sizer by diluting the sample using water as dispersant[13–17].

2.2.6.2. Percentage drug entrapment (PDE)

The entrapped Lecarnidipine within niosomes was determined after removing the unentrapped drug by dialysis. The dialysis was carried out by taking niosomal dispersion in dialysis bag, which was dipped in a beaker containing 400 ml of PBS with a pH of 7.4 the beaker was placed on a magnetic stirrer run for 4 h with a speed of 80- 120 rpm. Then, the solution inside the receptor compartment was studied for unentrapped drug. The PDE in the niosomes was calculated

from the ratio of the difference of the total amount of drug added and the amount of unentrapped drug detected, to the total amount of drug added[6,18–21].

2.2.6.3. Drug content determination

The amount of drug contained in Niosomal dispersion was determined by dissolving 100 ml of the formulation in 10ml of ethanol. The mixture was analysed for the drug content[22,23].

2.2.6.4. Transmission Electron Microscopy (TEM)

External morphology of prepared nanosuspension was determined using transmission electron microscopy. Sample of the niosomal dispersion was prepared by placing a drop onto a copper grid. Digital Micrograph and Soft Imaging Viewer software were used to perform the image capture and analysis, including particle size[24].

2.2.7. Formulation of Placebo patch, LCP patch and LCP loaded niosomal patch

Placebo patches were prepared by using various polymers as shown in table-2. LCP patch and LCP loaded niosomal dispersion is incorporated into the P7, P10 and P13 shown in table 3 & 4 and characterized. The prepared Niosomal formulations were incorporated into transdermal patch by solvent casting method using aluminium foil as a backing membrane. The various polymer combinations were weighed accurately and mixed in Chloroform: Methanol mixture stirred for 30min. Finally, the plasticizer (PEG-400) was dropped into the solution with stirring for more half an hour. Then the solution was kept aside overnight for clearance of all the bubbles. The next day, it was poured onto the Teflon plates set at room temperature and left over until uniformly dried film is obtained[25–30].

Table 2: Preliminary Placebo Patches

Placebo Formulation	**Polymers/ Film Forming agents** (Solvents: Methanol & Chloroform (1:1), Plasticizers: Glycerine: PEG 200 (1:1))					**Patch Characteristics**
	HPMC E5	HPMC 5CPS	HPMC 15 CPS	Carbopol 934	Sodium Alginate	
P1	500	-	-	-	-	Delicate film & showed poor ejection glass surface
P2	-	500	-	-	-	Very delicate film & showed poor ejection glass surface
P3	-	-	500	-	-	Brittle film
P4	-	-	-	500	-	Film tore off after ejection
P5	-	-	-	-	500	Dispersion time was above 30sec
P6	250	250	-	-	-	Very soft and sticky
P7	**250**	**-**	**250**	**-**	**-**	**Excellent, smooth and flexible**
P8	250	-	-	250	-	Patchy film
P9	250	-	-	-	250	Soft and too sticky
P10	**-**	**250**	**2-50**	**-**	**-**	**Excellent, smooth and flexible**
P11	-	250	-	250	-	Patchy film & tore off
P12	-	250	-	-	250	Soft and oily film
P13	**-**	**-**	**250**	**250**	**-**	**Excellent, smooth and flexible**
P14	-	-	250	-	250	Smooth but oily
P15	-	-	-	250	250	Film was soft and sticky
P7, P10 & P13 were found to be Good placebo patches						

Table 3: Formulation of Lecarnidipine Transdermal Patches

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lecarnidipine HCl (mg)	10	10	10	10	10	10	10	10	10
Polymers (mg)									
HPMC E5: HPMC 15 CPS	125	125	125	-	-	-	-	-	-
HPMC 5 CPS: HPMC 15 CPS	-	-	-	125	125	125	-	-	-
Carbopol 734: HPMC 15 CPS	-	-	-	-	-	-	125	125	125
Penetration enhancers (ml)									
Labrasol ALF	0.05	-	-	0.05	-	-	0.05	-	-
Transcutol	-	0.05	-	-	0.05	-	-	0.05	-
Span 60	-	-	0.05	-	-	0.05	-	-	0.05
Plasticizer (ml)									
PEG 200	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Glycerine	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Solvents (ml)									
Chloroform	3	3	3	3	3	3	3	3	3
Methanol	2	2	2	2	2	2	2	2	2

Table 4: Formulation of Lecarnidipine Loaded Niosomal Patches

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lecarnidipine Niosomal Dispersion (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Polymers (mg)									
HPMC E5: HPMC 15 CPS	125	125	125	-	-	-	-	-	-
HPMC 5 CPS: HPMC 15 CPS	-	-	-	125	125	125	-	-	-
Carbopol 734: HPMC 15 CPS	-	-	-	-	-	-	125	125	125
Penetration enhancers									
Labrasol ALF	0.05	-	-	0.05	-	-	0.05	-	-
Transcutol	-	0.05	-	-	0.05	-	-	0.05	-
Span 60	-	-	0.05	-	-	0.05	-	-	0.05
Plasticizer (ml)									
PEG 200	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Glycerine	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Solvents (ml)									
Chloroform	3	3	3	3	3	3	3	3	3
Methanol	2	2	2	2	2	2	2	2	2

2.2.8. Characterization of Prepared patches

2.2.8.1. Organoleptic Properties

The patches were evaluated for color, odor, uniformity of appearance, texture, smoothness, and softness by physical touch and visual observation, as these are some important criteria for assessing the intake acceptance of such delivery systems[31–33].

2.2.8.2. Thickness of the patch

The thickness of the film (required for 10 mg of drug dose delivery, with a dimension of 2 × 2 cm^2 at five different locations was determined using a Vernier calliper. The test was conducted thrice and the average value was recorded. Uniformity in the thickness of the film is a salient feature as it is directly related to the drug content uniformity of the film[34–36].

2.3.8.3. Folding Endurance

A film was folded and unfolded repeatedly at an identical location till it broke. The number of times the film was bent over on itself at a particular position without breaking was recorded as folding endurance. The experiment suggests the extent of flexibility or brittleness of the film[37–40].

2.3.8.4. Surface pH

The prepared patches were moistened with 0.5 ml of distilled water in a Petri dish for 30sec. The pH meter electrode was brought in touch with the surface of the film for 1 min, allowing equilibration. Then the pH value was recorded employing a digital pH meter. Three determinations were undertaken and the average value along with the standard deviation (SD) was recorded[41,42].

2.3.8.5. Percent Moisture Content

Accurately weighed patch was placed in a desiccator accommodating fused anhydrous calcium chloride for 3 days. Subsequently, the film was taken off the desiccator and weighed again. The % moisture content of the film formulation was calculated by the following formula. The study was conducted three times[41,43–45].

%Moisture content ¼ Initial Wt: −Final Wt: =Initial Wt: 100

2.3.8.6. Drug Content Uniformity

In this study, five patches were used, where each patch was kept into a volumetric flask of 100 ml individually and was completely dispersed in a little amount of PBS pH 6.8. Then the volume of the flasks was made up by the buffer itself and was positioned on a sonicator to get the drug completely dissolved. Through a membrane filter (0.45 µm), 1 ml of the solution was filtered and diluted up to 25 ml with the PBS again. The absorbance of this diluted solution was taken against PBS 6.8 as a blank employing a UV–visible spectrophotometer at λmax = 237 nm[46].

2.3.8.7. Invitro diffusion studies

The Franz Diffusion cell was used for invitro permeation study. The Franz Diffusion Cell is a simple, reproducible test for measuring the *in vitro* drug release from creams, ointments and gels. The Franz Cell consists of two primary chambers separated by a membrane. The test product is applied to the membrane via the top chamber- donor compartment. The bottom chamber- receptor compartment contains fluid from which samples are taken at regular intervals for analysis. This testing determines the amount of active drug that has permeated the membrane at each time point. The cellophane membrane was mounted on a diffusion cell assembly with an effective diffusion area of 2.303 cm^2. The receptor compartment consisted of a 22.5 ml phosphate buffer at pH 6.8 as the receptor fluid agitated at 100 rpm, and was maintained at 37 ± 0.5°C throughout the experiments. The cumulative amount that permeated across the cellophane membrane was calculated and plotted against time[47–50].

2.3.8.8. Kinetic analysis of diffusion data: The in vitro permeation data of optimized formulations was analysed by fitting the release data into various kinetic models to elucidate permeation profile[51,52].

2.3.8.9. Ex-vivo permeation study: Ex vivo permeation studies are conducted by using Franz diffusion apparatus to forecast the in vivo absorption of the drug. The Pig abdominal skin cleaned and extraneous tissues and subcutaneous fat was removed with the scalpel from the excised skin. was kept between the diffusion cells, with stratum corneum facing the donor compartment. The patch is applied above the stratum corneum (upper side) and a dialysis membrane was kept over the patch. The receiver phase (lower phase) was containing 22.5 ml of Phosphate buffer (pH 6.8) stirred at 500 rpm on a magnetic stirrer. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The amount of the drug transferred was estimated by taking 5ml of the sample at graded time intervals up to 24 hrs. The absorbance was measured at 237 nm spectrophotometrically. The graph was plotted between Cumulative amounts of drug transferred in µg/cm2 against time[46,53].

3. RESULTS

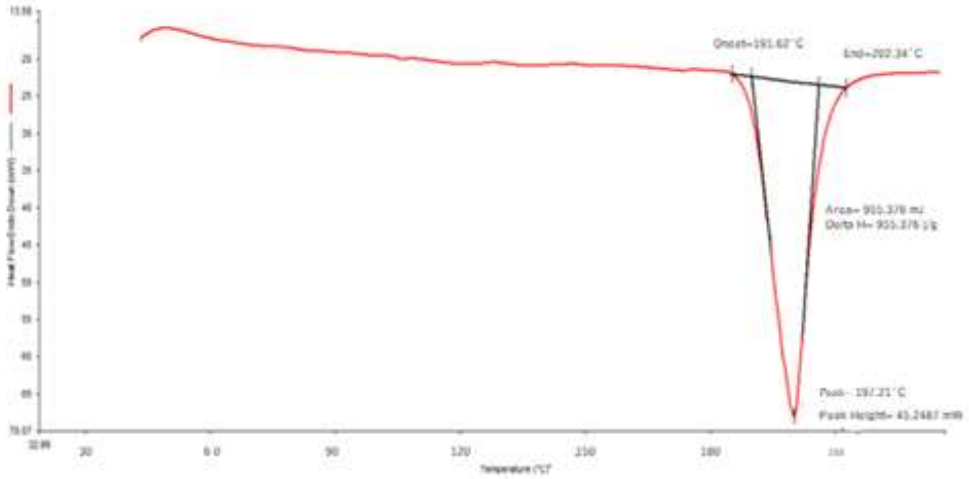

Figure 2: DSC graph of Lecarnidipine hydrochloride

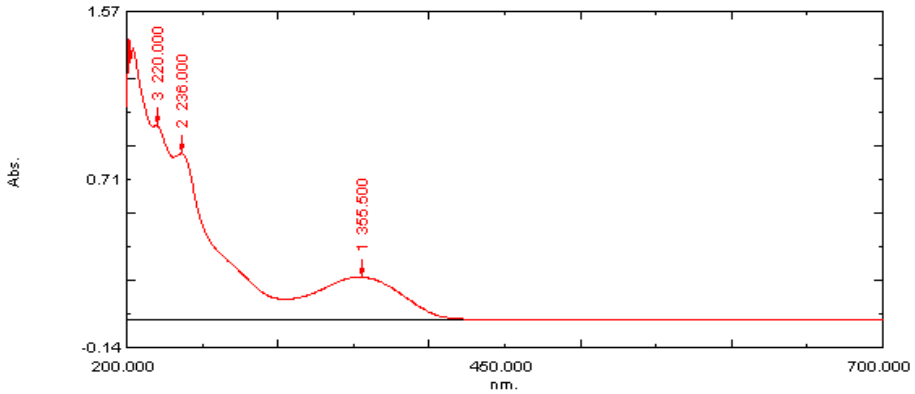

Figure 3: UV-Spectra of Lecarnidipine hydrochloride

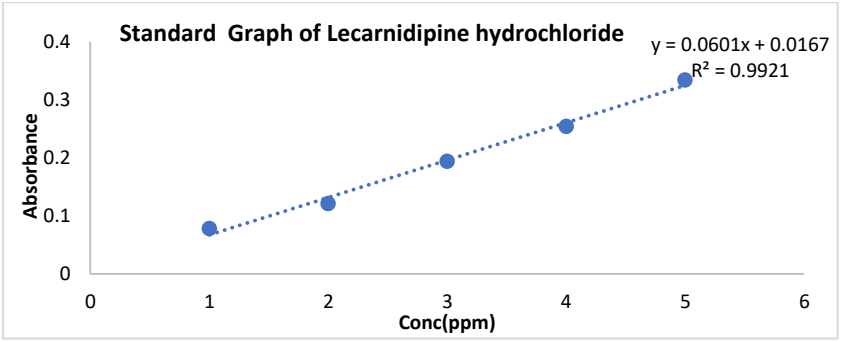

Figure 4: Calibration curve of Lecarnidipine hydrochloride

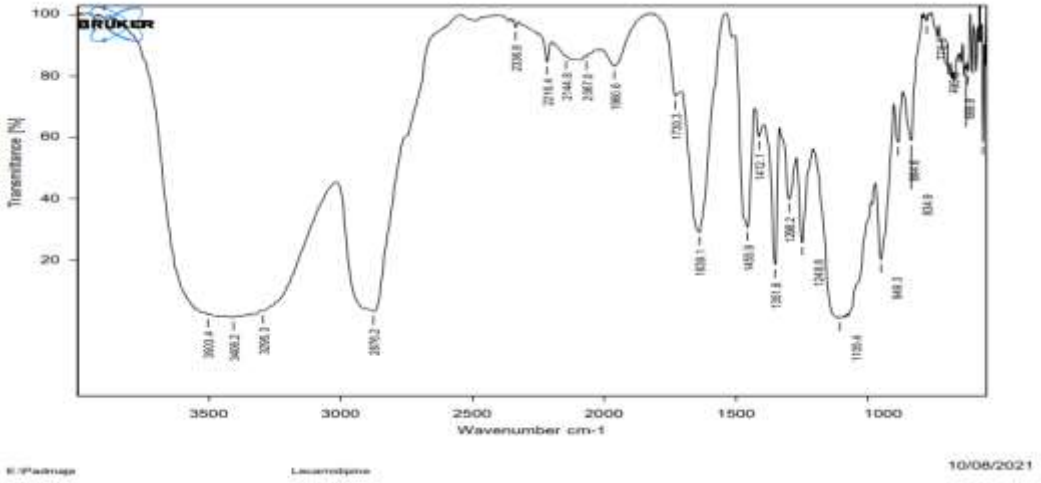

Figure 5: FTIR spectra of Lecarnidipine hydrochloride

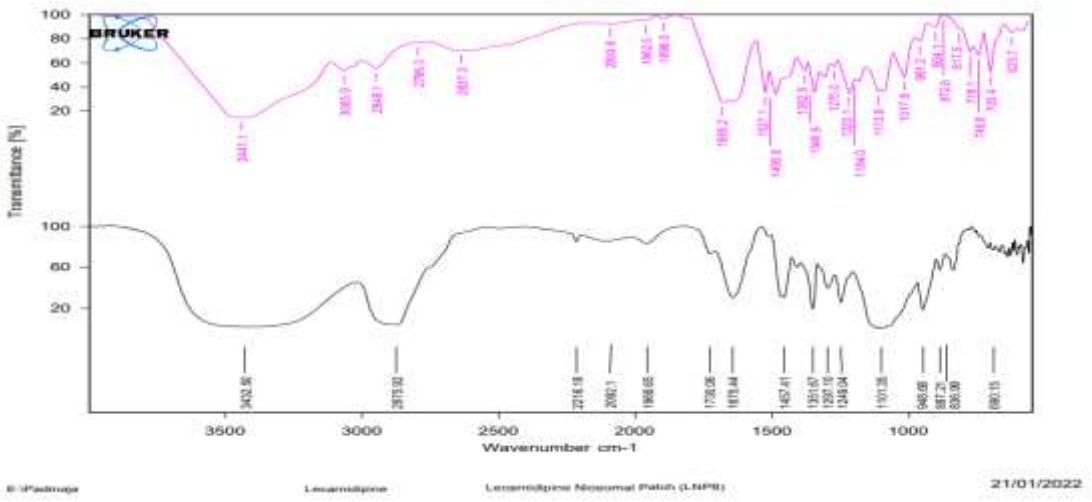

Figure 6: FTIR spectra of LCP Niosomal dispersion

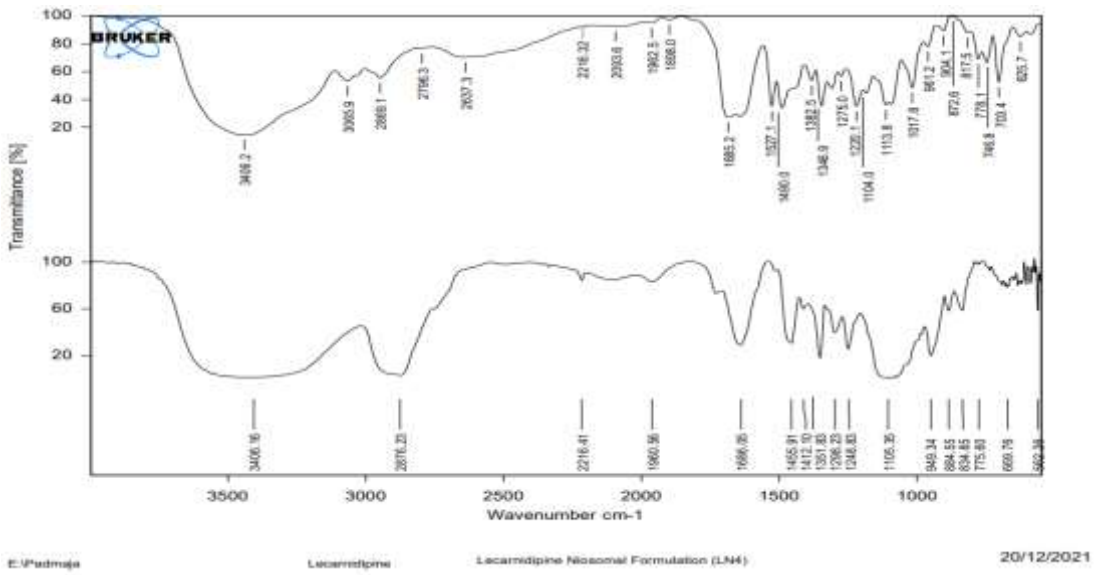

Figure 7: FTIR spectra of LCP Niosomal patch

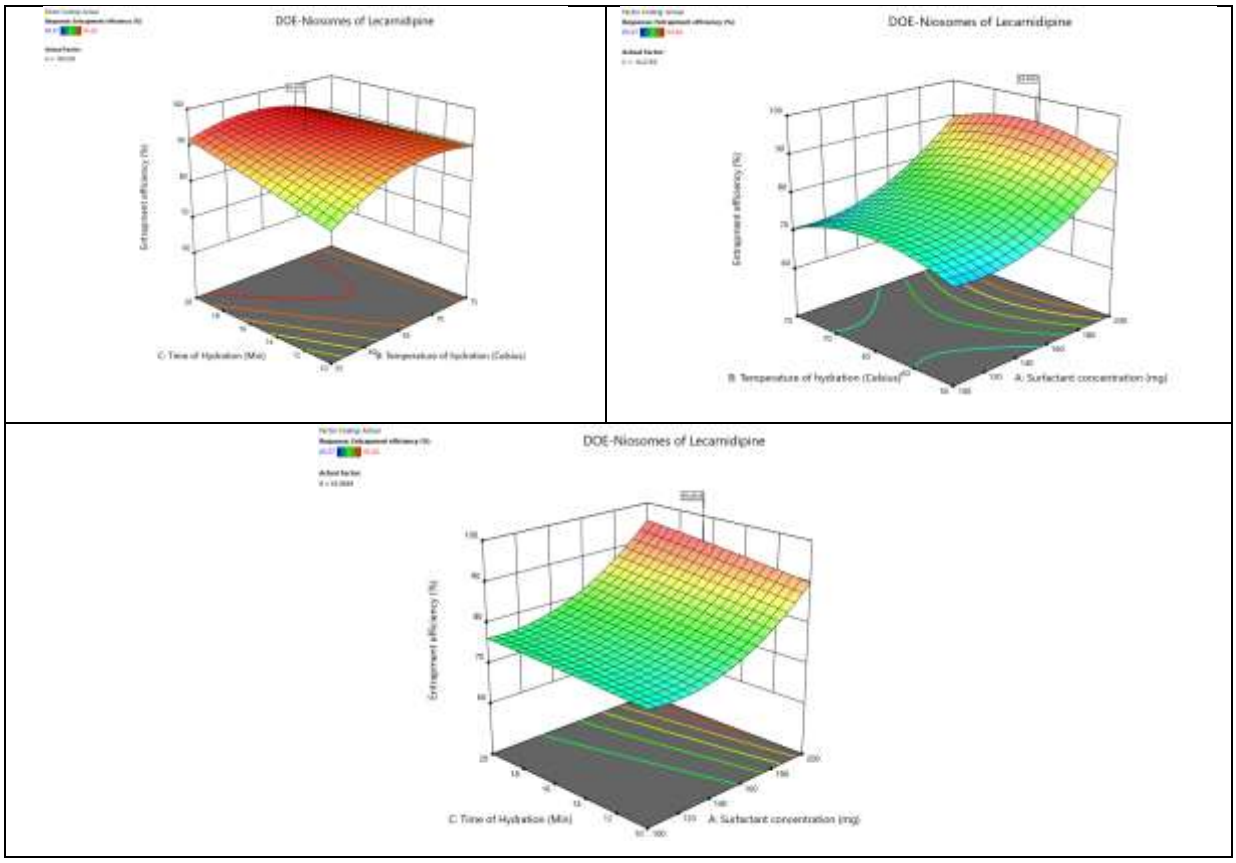

Figure 8: DoE 3D graphs of Lecarnidipine Niosomes

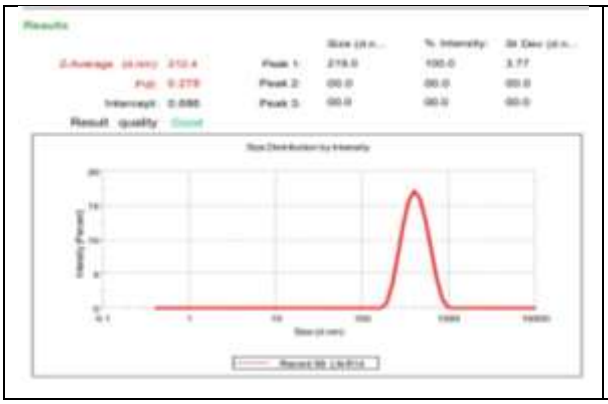

Figure 9: Size and PDI of LN-R14

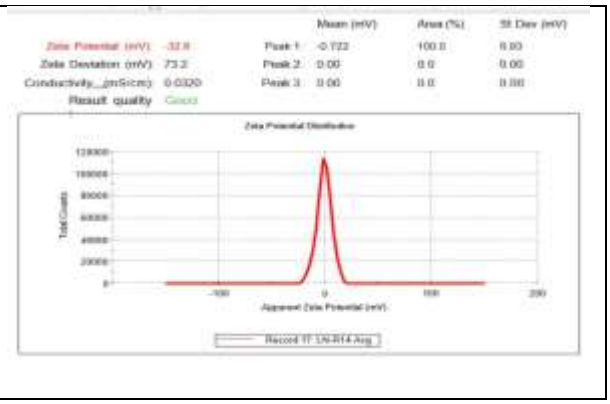

Figure 10: Zeta potential of LN-R14

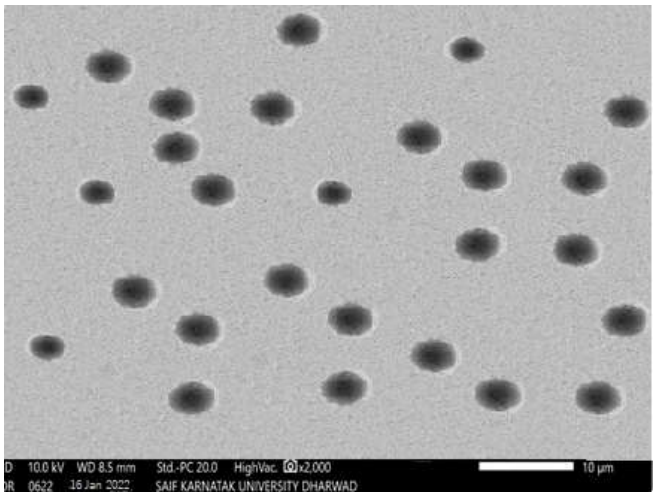

Figure 11: TEM image of LN-R14

4. DISCUSSION

The purity was checked by DSC and melting point (MP) was obtained at 197.21°C shown in the Fig-2. The UV-scan spectrum and calibration curve of Lecarnidipine hydrochloride developed by HPLC was linear with R2 value 0.9991 shown in the Fig-3 & 4. The drug- excipients compatibility showed all the excipients were compatible with the drug shown in the Fig-5,6 & 7. In the present research work Lecarnidipine niosomes were prepared using various non-ionic surfactants (Span 40, Span 60, Span 80, Tween 40, Tween 60 and Tween 80) along with cholesterol and soya lecithin to stabilize the formed niosomes in different proportions by the thin film hydration method by CCD shown in Fig-8. The prepared Lecarnidipine niosomes were evaluated for various parameters like particle size, Poly dispersibility index, zeta potential, entrapment efficiency and *drug content*. The LN-R14 niosomal formulation was considered as an optimised dispersion with a least size (212.4 nm) among all the formulations with good PDI (0.278) and zeta potential (32.6 mV) shown in Fig-9&10. LN-R14 formulation showed good entrapment efficiency and drug release. Transmission electron microscopy analysis shown the niosomes were spherical and in nano range.

The daily dose of LCP in patches selected is 10mg and each circular patch of 2 × 2 cm^2 patch contain 10 mg of LCP. The best placebo patches combinations were used for further studies, the evaluated for various parameters and the best niosomal patch LNT8 shown Weight Variation (373±56.8mg), thickness (0.379±0.08mm), % moisture content (0.96±0.01), folding endurance (>200), drug content (99.81±1.92) and surface pH (6.69±0.11). Invitro diffusion studies shown LNT8 released upto 24 hours with %CDR of 99.27% and the drug diffusion data is fitted into various mathematical models and LNT8 followed zero order drug release kinetics and the diffusion mechanism was non-fickian diffusion depicted in the table-5. From the ex-vivo permeation studies Q_{24} (9912±189 µg/cm^2), Flux (3.72± 0.83 µg/cm^2/min), Permeation Coefficient (0.372 cm/hr) & Lag time (>15 min).

Table 5: Drug Release Kinetic Studies of LNT8

Formulation code	Zero order	First order	Hixon & Crowells	Higuchi	Korsemeyer-Peppa's equation		Diffusion mechanism
	R^2	R^2	R^2	R^2	R^2	n	
LNT8	0.9932	0.8297	0.8524	0.9321	0.9465	1.1513	Non-Fickian diffusion

5. CONCLUSION

Lecarnidipine hydrochloride is BCS class drug with low solubility and its niosomes are good carries to cross the barrier and make the drug available in the systemic circulation. The Lecarnidipine niosomes has been successfully incorporated into the transdermal patch by using HPMC E5 and HPMC 15cps. Lecarnidipine niosomal patch containing 10mg of dose will be released upto 24 hours. The patch will sure enhance patient compliance in chronic hypertension.

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