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Development And Characterization Of Niosomal Transdermal Formulation Loaded Lecarnidipine Hydrochloride

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ABSTRACT:
Introduction and Background: For several medications, matrix-based transdermal formulations have been created. Derma as a delivery system for medicinal agents has recently seen a renaissance as a viable option for both local and systemic drug delivery. The current work set out to design and evaluate transdermal medication delivery patches based on niosomes as its aim and objectives.
Material and Methods: An improved formulation of LCP nanoparticles with a polydispersity index and a particle size of 225 nm was achieved using solvent evaporation. Using solvent casting techniques, LCP patches were prepared by dispersing nanoparticles in a variety of polymers and sodium alginate concentrations. The patches were then optimized using a central composite design. In-vitro drug release studies and ex-vivo skin permeation studies were conducted.
Results: A member of the BCS class of drugs, lecarnidipine hydrochloride has a poor solubility but, because to its niosomes, is able to pass the blood-brain barrier and enter the bloodstream. The transdermal patch now contains lecarnidipine niosomes, which were successfully integrated utilizing HPMC E5 and HPMC 15cps. A lecarnidipine niosomal patch with a 10 mg dosage released its contents more quickly.
Conclusion: The study's findings indicated that the P10 patch formulation was the most effective. If a patient has persistent hypertension, the patch will increase their compliance without a doubt.

Keywords: Niosomes, transdermal, drug delivery, patch, drug release.

INTRODUCTION:

Medication delivery systems that enter the bloodstream through the skin have gained a lot of attention in the past decade. Particularly compared to conventional dosage forms and oral controlled release systems, transdermal drug delivery systems offer numerous benefits, such as avoiding hepatic first pass metabolism, reducing administration frequency, minimizing gastrointestinal side effects, and increasing patient compliance [1-3]. There are a number of drugs that have matrices-based transdermal preparations. Derma administration of medicinal compounds is making a comeback as a potential approach for both local and systemic medicine delivery. This approach has many advantages over oral drug delivery, including as more widespread acceptability, no first-pass metabolism, longer drug delivery times, more consistent delivery profiles, less variation between and within patients, and the option to discontinue treatment if needed [2-7]. To circumvent the skin's protective barrier, researchers developed second-generation transdermal drug delivery systems. Iontophoresis, a noncavitational ultrasonic method, or conventional chemical enhancers like azone and SEPA were utilized in these systems [8-11]. A potent antihypertensive and antianginal medicine, lercanidipine hydrochloride was selected as the study's model drug. The rationale for choosing lercanidipine hydrochloride includes the following: the drug's high absolute bioavailability of approximately 10% due to its long half-lives and extensive first pass metabolism; and the drug's complete and aberrant absorption from the gastrointestinal tract following an oral dose of 10–20 mg [12-15]. Peak plasma concentrations of lercanidipine occur one to three hours following oral treatment, indicating limited absorption. The liver undergoes extensive processing, making around 44% of it accessible. Cytochrome P450 isoenzyme 3A4 is the principal metabolite of lercanidipine hydrochloride [16-18]. A half-life of about

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4.6 hours is observed for lecanidipine. The low therapeutic dose and considerable biotransformation in the liver of lercanidipine hydrochloride (HCl) make it an ideal candidate for the development of transdermal therapy devices. An important part of hypertension management is maintaining blood pressure, and lercanidipine HCl transdermal formulations provide this for a long time [19-20]. The present investigation set out to design and evaluate niosome-based transdermal medicine delivery patches.

MATERIALS AND METHODS:
Purchasing lecarnidipine from a pharmaceutical company in India. Loba Chemicals Private Limited of Mumbai, India, supplied all the other excipients used in the study. Each and every solvent that was used in this study was an analytical solvent.

Pre-formulation study:
Analyzing Features Vividly Shimadzu Corporation Japan underwent a calorimetry analysis to confirm the drug's purity. A nitrogen gas flow with a temperature range of 25 to 450°C was used to heat the pharmaceutical sample in sealed aluminum pans at a rate of 5°C/min [21].

Analytical Method Development:
A 100 mL volumetric flask was filled with 100 mg of lecarnidipine hydrochloride. Twenty milliliters of methanol was used to dissolve the drug, and one hundred milliliters of the same distilled water was added. The finished solution was called "stock" since its concentration was 1 mg/ml. A solution with a concentration of 100 micrograms per milliliter was prepared by diluting 10 milliliters of this stock solution with 100 milliliters of methanol. A variety of concentrations of lecarnidipine hydrochloride solution were prepared by diluting this second solution. In order to determine their absorbance, the solutions were subjected to a UV spectrophotometer measurement between 200 and 800 nm, using a blank as a control [22-23].

Drug excipients compatibility:
Spectrophotometer readings of the potassium bromide pellet technique were used to acquire the Fourier-transform infrared spectra of the moisture-free powdered material. Scanning was carried out at 4000-400 cm-1 with a resolution of cm-1. Just like that, for the medicine and each excipient in the formulation [24].

Preparation of Niosomes:
Surfactants having the highest LCP solubility were utilized in the formulation of niosomes. Surfactants were introduced into a round-bottom flask. Subsequent to the incorporation of the solvent system, the mixture is manually agitated to facilitate the dissolution of the components in the solvent (methanol and chloroform). The flask was secured to a revolving evaporator, immersed in a water bath maintained at 60˚C, and rotated for 45 minutes at 100 rpm. A slender layer was observed developing at the base. A 6.8 pH buffer is utilized to hydrate the thin film. The resultant solution was subjected to sonication in a bath sonicator for ten minutes. Table 1 presents the various surfactant compositions for the niosomal dispersion formulations [10, 25-28].

Table 1: Composition of Niosomal formulation

Batches	Excipient	Lercanidipine (mg)	Surfactant (mg)	Cholesterol (mg)	Soya Lecithin	Solvent Ratio	Buffer
B1	Span 40	150	200	150	60	2:2	5ml
B2	Span 40	150	100	150	150	2:2	5ml
B3	Tween 40	150	100	150	150	2:2	5ml
B4	Tween 60	150	100	150	150	2:2	5ml
B5	Tween 80	150	100	150	150	2:2	5ml
B6	Span 60	150	200	150	150	2:2	5ml
B7	Span 60	150	200	150	150	2:2	5ml
B8	Span 80	150	100	150	150	2:2	5ml
B9	Tween 40	150	100	150	150	2:2	5ml
B10	Tween 60	150	100	150	150	2:2	5ml
B11	Span 60	150	200	150	150	2:2	5ml
B12	Span 60	150	200	150	150	2:2	5ml

Characterization of Niosomes:
Particle size, PDI and ZP:
Verifying vesicle size, polydispersity index, and zeta potential after diluting the material with water as a surfactant, the PDI, zeta potential, vesicle size, and yield of the generated Niosomes were determined using laser diffraction and the

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Malvern Master sizer [29-33].

% drug entrapment:
The amount of Lecarnidipine that was entrapped in the niosomes was determined after the drug was removed from them using dialysis. A dialysis bag containing niosomal dispersion was submerged in 400 cc of pH 7.4 PBS. A magnetic stirrer was used to spin the beaker at a speed of 80 to 120 rpm for four hours. Then, the drug that was not caught was checked in the receptor compartment's solution. Niosome PDE was calculated as the ratio of the amount of drug added to the total amount of drug minus the amount of unentrapped drug, divided by the total amount of drug [34].

Transmission Electron Microscopy:
The surface morphology of the produced nanosuspension was examined using transmission electron microscopy. To get a sample of the niosomal dispersion, a copper grid was utilized. Soft Imaging Viewer and Digital Micrograph were utilized for the picture capture and processing, which included particle size analysis [35-37].

Formulation of patch:
Table 2 lists the various polymers utilized in the production of the placebo patches. A description and integration of the P7, P10, and P13 from Tables 3 and 4 with an LCP patch and an LCP loaded niosomal dispersion have been provided. The Niosomal formulations were applied to transdermal patches using the solvent casting technique, with aluminum foil serving as the backing membrane. A solution of chloroform and methanol was prepared by carefully weighing, mixing, and agitating the various polymer combinations for 30 minutes. After another half an hour of stirring, the plasticizer was finally added to the mixture. The next step was to let the mixture sit overnight so that the bubbles may pop. The film was allowed to dry evenly before being transferred the next day on Teflon plates held at room temperature [34-38].

Characterization of formulated patch:
Characteristics of Systems for Evaluating Odor The color, smell, texture, smoothness, and softness of the patches were assessed by eye inspection and physical contact. The extent to which the body absorbs such delivery techniques is dependent on these and other critical parameters [39].

Thickness of the patch:
At five separate sites with a 2 × 2 cm2 dimension, the film thickness required to administer a dose of 10 mg of medication was determined using a Vernier calliper. Following three repetitions of the exam, the mean outcome was recorded. Having a consistent thickness is a prominent attribute of the film because it directly affects the consistency of the pharmaceutical content [40].

Folding Endurance:
Over and over again, the same place was used to fold and unfurl a film until it finally snapped. The folding endurance of a film was determined by counting how many times it could be folded at a certain angle without rupturing. The film's brittleness or flexibility is shown by the experiment [41].

Percent Moisture Content:
A precisely weighed patch was placed in a desiccator containing fused anhydrous calcium chloride for a duration of three days. Next, the film was taken out of the desiccator and weighed again. The percentage moisture content of the film formulation was determined using the following formula [18-20].

Drug Content Uniformity:
Five patches were utilized in this investigation. Each patch was placed in its own 100 ml volumetric flask and thoroughly mixed with a little amount of PBS with a pH of 6.8. After that, the buffer was used to fill up the flasks to their full amount, and then they were placed on a sonicator to ensure that the drug was dissolved thoroughly. After passing 1 milliliter of the solution through a membrane filter, it was further diluted with 25 milliliters of PBS. The absorbance of this watered-down solution was measured at λmax = 237 nm using a UV-visible spectrophotometer, with PBS 6.8 serving as a control [39-42].

RESULTS AND DISCUSSION:
Pre-formulation study:
The purity of the medicine was checked using the melting point apparatus, which was operated on by Shimadzu Corporation Japan. The melting point was determined to be 197.21°C, and the purity was verified using DSC.

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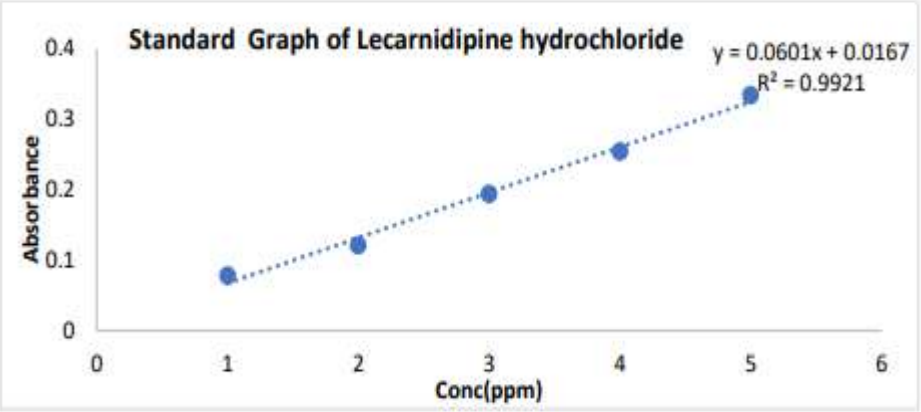
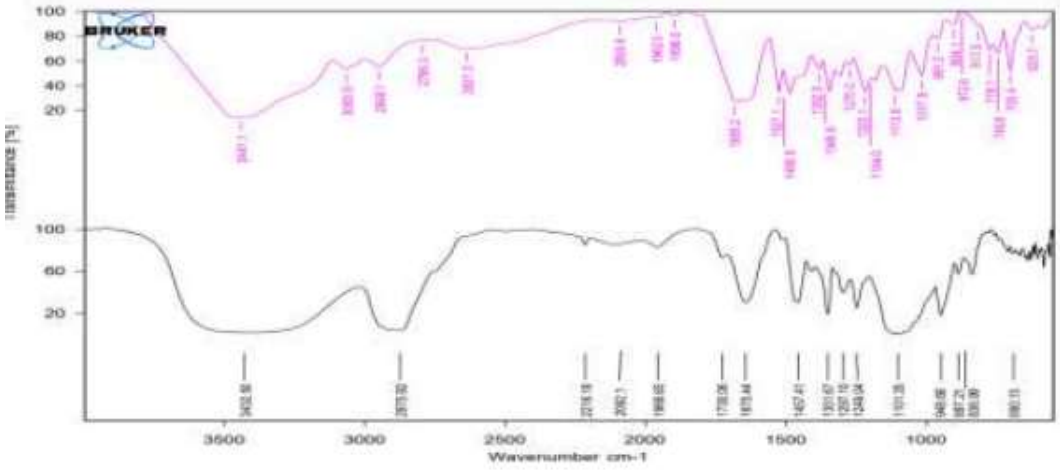
Analytical Method Development:
Lecarnidipine hydrochloride, 100 milligrams, was carefully placed to a 100 milliliter volumetric flask. The medication was dissolved in 20 mL of methanol, and then the same volume of distilled water was added to bring it up to 100 mL. In contrast to a blank, the absorbance of the solutions that were so made was measured using a UV spectrophotometer within the 200-800 nm range. As shown in figure 1, the HPLC-developed calibration curve and UV-scan spectra of lecarnidipine hydrochloride were linear with an R2 value of 0.9991.

Figure 1: Lecarnidipine hydrochloride UV-Spectra



Drug excipients compatibility:
The spectrophotometer was calibrated using the potassium bromide pellet method to acquire the Fourier-transform infrared spectra of the moisture-free powdered sample. The resolution was cm-1, and the scanning was done at 4000-400 cm-1. According to the results of the drug-excipients compatibility test, all of the excipients displayed in Figure 2 were suitable for use with the drug [22-24].

Figure 2: Study on drug excipient compatibility



Preparation of Niosomes:
The rotary evaporator was used to spin the flask at 100 rpm for 45 minutes while it was submerged in a water bath kept at 60˚C. At the base, a thin coating was noticed to be forming. Using a buffer with a pH of 6.8, the thin film is hydrated. After that, we sonicated the mixture for 10 minutes in a Bath sonicator. The current study used the thin film hydration approach to create lecarnidipine niosomes with varying concentrations of non-ionic surfactants, cholesterol, and soya lecithin for stabilization.

Characterization of Niosomes:
Particle size, PDI and ZP:
The synthesized Niosomes' vesicle size, polydispersity index (PDI), and zeta potential were ascertained using laser diffraction with the use of the Malvern Master sizer. Several metrics were used to assess the manufactured Lecarnidipine niosomes, including drug content, zeta potential, entrapment efficiency, and polydispersibility index. Figure 3 shows that out of all the formulations, the optimized niosomal formulation had the best zeta potential (-12.5 mV) and PDI

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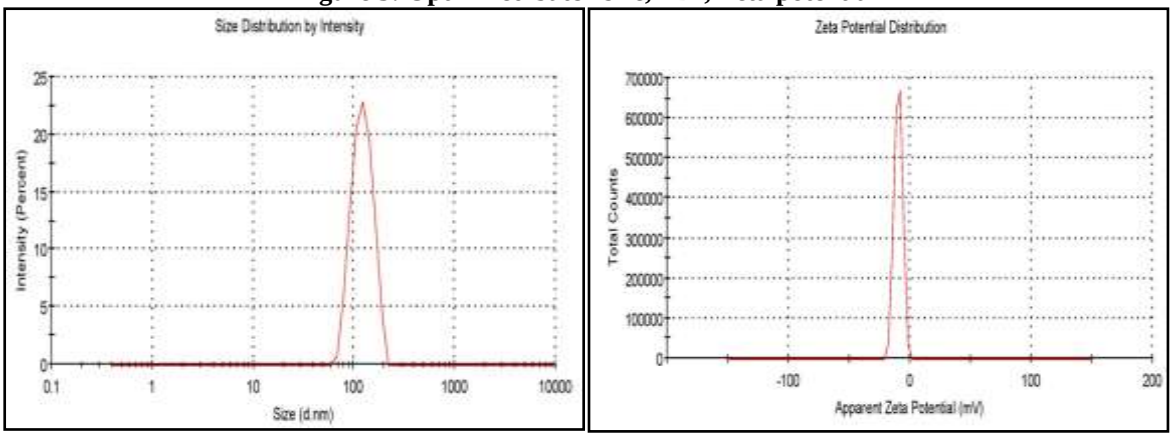
(0.348), and it also had the smallest size (120.5 nm) [24-26].

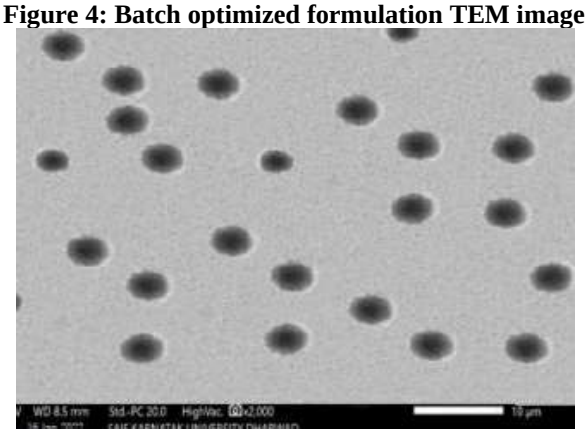
Figure 3: Optimized batch size, PDI, Zeta potential



Percentage drug entrapment:
To do the dialysis, niosomal dispersion was added to a dialysis bag. The bag was then submerged in 400 ml of PBS, which had a pH of 7.4. The beaker was then set on a magnetic stirrer set to spin for 4 hours at a speed of 80-120 rpm. After that, the unentrapped drug's solution within the receptor compartment was examined. The PDE in the niosomes was determined by dividing the sum of the drug additions by the sum of the drug amounts and the quantity of unentrapped drug found. The drug release and entrapment efficiency were both good in the improved formulation batch [25-42].

Transmission Electron Microscopy:
Transmission electron microscopy was used to determine the external morphology of the produced nanosuspension. A copper grid was used to prepare a sample of the niosomal dispersion. Particle size analysis and image capture were carried out using Digital Micrograph and Soft Imaging Viewer software. Figure 4 shows the results of the transmission electron microscopy study, which demonstrated that the niosomes were nanosized and spherical.

Figure 4: Batch optimized formulation TEM image



Formulation of Transdermal patch:
It incorporates the patch and niosomal dispersion filled with LCP. Using the solvent casting process and aluminum foil as a backing membrane, the Niosomal formulations that were synthesized were integrated into a transdermal patch. Precise weighing and mixing in Chloroform of the different polymer combinations: Stir the methanol mixture for half an hour. The last step was to add the plasticizer to the mixture while stirring it for at least 30 minutes. After that, the solution was set aside for the night to allow the bubbles to pop. It was left to dry uniformly on Teflon plates that had been left out at room temperature the day before. Each circular patch measuring 2 × 2 cm2 contains 10 mg of the prescribed LCP daily dose. Table 2 contains the formula for niosomal patches filled with lecarnidipine.

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Table 2: Lecarnidipine-Loaded Niosomal Patches

Code	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Lecarnidipine Niosomes	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Polymers (mg)										
HPMC E5: HPMC 10 CPS	125	125	125	-	-	-	-	-	125	125
Carbopol 734: HPMC 10 CPS	-	-	-	-	-	-	125		-	125
Penetration enhancers										
Span 60	-	-	0.05	-	-	0.05	-	-	0.5	0.05
Transcutol	-	0.05	-	-	0.05	-	-	0.05	-	-
Labrasol ALF	0.05	-	-	0.05	-	-	0.05	-	-	-
Plasticizer (ml)										
Glycerine	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
PEG 200	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Solvents used (in ml)										
Methanol	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Chloroform	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Characterization of formulated patch:

Organoleptic Properties:

Important criteria for evaluating the intake acceptance of such delivery methods include color, odor, consistency of appearance, texture, smoothness, and softness of the patches, which were assessed by physical touch and visual inspection.

Thickness of the patch:

Using a Vernier calliper, the thickness of the film needed to give 10 mg of drug dosage at five separate sites was measured. The film had a 2 × 2 cm2 dimension. The test was repeated three times, with the mean value being recorded each time. A notable quality is the film's homogeneity in thickness, which is associated with the uniformity of the drug content.

Folding Endurance:

At the same spot, a film was folded and unfolded till it snapped. The folding endurance of a film was measured by counting how many times it could be bent over in a specific position without breaking. The experiment provides insight into the film's pliability or fragility to varying degrees. The improved patch P10 had a folding endurance of more than 200.

% Moisture Content:

After three days in a desiccator that could accommodate fused anhydrous calcium chloride, the precisely weighted patch was removed. We next removed the film from the desiccator and gave it another weighing. We used the following formula to determine the film formulation's moisture content in %. The research was carried out three times, and the final result showed a moisture content of 0.95±0.14.

Drug Content Uniformity:

Five patches were utilized in this investigation. Each patch was placed in its own 100 ml volumetric flask and thoroughly mixed with a little amount of PBS with a pH of 6.8. After that, the buffer was used to fill up the flasks to their full amount, and then they were placed on a sonicator to ensure that the drug was dissolved thoroughly. After passing 1 milliliter of the solution through a membrane filter, it was further diluted with 25 milliliters of PBS. The absorbance of this watered-down solution was measured at λmax = 237 nm using a UV-visible spectrophotometer, with PBS 6.8 serving as a control. The optimized medication content patch P10 had a value of 98.92±2.17.

CONCLUSION:

Although lecarnidipine hydrochloride, which belongs to the BCS class of medicines, has a low solubility, it is able to cross the blood-brain barrier and enter the bloodstream due to the presence of niosomes. Using HPMC E5 and HPMC 15cps, lecarnidipine niosomes were successfully integrated into the transdermal patch, which now contains the niosomes. Over the course of twenty-four hours, the lecarnidipine niosomal patch, which has a dose of ten milligrams overall, will be administered. It is without a doubt that the patch will boost a patient's compliance with their medication regimen if they have persistent hypertension.

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Conflict of Interest
None

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