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Original Article

A Box Behnken Design Optimized Nano Vesicular Transdermal Patch for Allergies

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ABSTRACT

Background: The work aimed to fabricate Loratadine (LRD) niosomes by employing a Box Behnken Design (BBD) and they were subsequently applied to transdermal patches utilizing BBD's solvent casting process. **Materials and Methods:** The prepared niosomes were assessed for their size, shape, zeta potential, and level of entrapment efficiency. The niosomal formulations that have been optimized were inserted into a patch system. Then, physico-chemical characteristics, and *in vitro* permeation studies were used to characterize each patch. **Results:** In comparison patches loaded with niosomal vesicles showed better drug release compared to the control patches. Niosomal patches had higher permeation than control patches, it was discovered. The surfactant in niosomes acts as a penetration enhancer, which helps to improve LRD permeation from niosomes. **Conclusion:** The work summarizes that the transdermal patches based on niosomes could efficiently deliver LRD medicines trans-dermally while preventing GIT side effects.

Keywords: Design, Kinetics, Loratadine, Niosomes, Patch, Permeation, Release.

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INTRODUCTION

Transdermal delivery offers several advantages over conventional drug delivery as they avoid first-pass metabolism in the liver and improve patient comfort and compliance.[1] A great deal of investigation made on the transdermal route for the delivery of niosomal drugs.[2]

A second-generation H1 histamine antagonist called Loratadine (LRD) is used to treat allergies. It is a BPS-II class drug that needs enhancement in solubility for its absorption and bioavailability.[3]

Niosomes have been researched as potential drug delivery platforms for a variety of routes, including transdermal, cutaneous, and oral. Niosomes have a remarkable capacity to entrap hydrophilic, lipophilic, and amphiphilic compounds. In terms of durability, cost, and simplicity of formulation. Transdermal patches are one of the cutting-edge pharmaceutical dosage forms for quickly transferring drugs from the skin to the bloodstream. The patches are designed to release medications at a specified rate in a controlled, modified, and time-limited way.[4,5]

Traditional research approaches usually study the influence of one flexible at a time due to its feasibility to manipulate statically and to the fact that only one variable can be studied at a time. As these two factors are interdependent, combining them will yield false results. A Design of Experiments (DOE) is essential for multivariate analysis. Typically, this means that only certain factors are included in the agreement. The authors used Design Expert (V.11) software to test % LRD release as a response to polymer concentration.[6]

MATERIALS AND METHODS

Materials

Cipla Ltd., Bengaluru, provided loratadine. The subsequent ingredients came from Merck: Cholesterol, span 40/60/80, dichloromethane, dicetyl phosphate. In the lab, double-distilled water and a buffer (pH-6 and 7.4) were made.

Saturation solubility of LRD

At 37°C, the saturation solubility of LRD in PBS (pH 7.4) and PBS containing 20% isopropyl alcohol were both investigated. In a 25 mL beaker with 10 mL of each solvent, extra LRD was added. The beakers were tightly covered and stirred for 24 hr at 37°C and 100 rpm in a shaker incubator.[7] LRD saturation concentration was assessed by HPLC analysis following the removal of aliquots from the solution, filtration, and 15 min of centrifugation at 1400 rpm.

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Preparation of the LRD niosomes

The ether injection technique was used to create Loratadine Niosomes (LN) (25 formulations). The cholesterol was dissolved in dichloromethane; Span-40, Span-60, and Span-80 were then dissolved in 16 mL of diethyl ether and combined with 4 mL of methanol containing a measured quantity of LRD. Dicetyl Phosphate (DCP) was then added to the mixture as needed. The produced solution was lastly gently injected into 20 mL of PBS (pH 7.4) using a syringe pump at a rate of 1 mL/min. Then, a magnetic stirrer was used to stir the solution continuously while maintaining the temperature between 60-65°C. The temperature variations between the phases caused evaporation, which resulted in the formation of niosomes (Table 1).[8]

Purification of drug-loaded niosomes

Drug-loaded niosomes were purified to eliminate the free drug from the niosomal suspension by employing a dialysis membrane technique. This was accomplished by completely moistening the Hi-media dialysis membrane by submerging it in saline solution for 2 hr prior to dialysis. After placing LRD-loaded niosomal vesicles in a dialysis bag, 200 mL of phosphate buffer (pH 7.4) was added. The receiver medium was stirred with a magnetic stirrer at 500 rpm. 5 mL of the sample was taken out at regular intervals and replaced with an equivalent volume of a new medium. Then spectrophotometric analysis was used to calculate the amount of free drug. Purification time was decreased by applying a statistical paired *t*-test with a 5% level of significance.[9]

Evaluation

The prepared LN were assessed for the following constraints.

Particle Size (PS) and Zeta Potential

Niosome PS and ZP were assessed as per Zetasizer nano user manual (Man0485-1.1). The outcomes of three distinct experiments were given as mean standard deviation. Electrophoretic Light Scattering (ELS) was used to detect the surface charge of the particles in order to calculate the ZP of the niosomes. The niosomes were dissolved in distilled water and

Table 1: Various formulations of LN.

Formulation	LRD (mg)	A: Cholesterol (mg)	B: Span 40 (mg)	C: Span 60 (mg)	D: Span 80 (mg)	DCM (mL)	Dicetyl phosphate (mg)	PBS (pH 7.4)
LN-1	100	50	25.0	37.5	37.5	10	5	q.s.
LN-2	100	100	25.0	37.5	37.5	10	5	q.s.
LN-3	100	50	50.0	37.5	37.5	10	5	q.s.
LN-4	100	100	50.0	37.5	37.5	10	5	q.s.
LN-5	100	75	37.5	25.0	25.0	10	5	q.s.
LN-6	100	75	37.5	50.0	25.0	10	5	q.s.
LN-7	100	75	37.5	25.0	50.0	10	5	q.s.
LN-8	100	75	37.5	50.0	50.0	10	5	q.s.
LN-9	100	50	37.5	37.5	25.0	10	5	q.s.
LN-10	100	100	37.5	37.5	25.0	10	5	q.s.
LN-11	100	50	37.5	37.5	50.0	10	5	q.s.
LN-12	100	100	37.5	37.5	50.0	10	5	q.s.
LN-13	100	75	25.0	25.0	37.5	10	5	q.s.
LN-14	100	75	50.0	25.0	37.5	10	5	q.s.
LN-15	100	75	25.0	50.0	37.5	10	5	q.s.
LN-16	100	75	50.0	50.0	37.5	10	5	q.s.
LN-17	100	50	37.5	25.0	37.5	10	5	q.s.
LN-18	100	100	37.5	25.0	37.5	10	5	q.s.
LN-19	100	50	37.5	50.0	37.5	10	5	q.s.
LN-20	100	100	37.5	50.0	37.5	10	5	q.s.
LN-21	100	75	25.0	37.5	25.0	10	5	q.s.
LN-22	100	75	50.0	37.5	25.0	10	5	q.s.
LN-23	100	75	25.0	37.5	50.0	10	5	q.s.
LN-24	100	75	50.0	37.5	50.0	10	5	q.s.
LN-25	100	75	37.5	37.5	37.5	10	5	q.s.

sonicated at 25°C to produce a transparent solution. The data were presented as the mean SD after each experiment was carried out three times.[10]

LRD Entrapment Efficiency (EE)

Since the entire LRD has never been contained by a dispersion (LN), free LRD is always present in the LN. 0.1 g of LN was soaked with 10 mL of PBS (pH 7.4) and sonicated in a bath sonicator for 10 min to separate the free LRD. A supernatant solution from the centrifugation of the LN at 10,000 rpm for 30 min at 25 ± 0.1°C was filtered to remove the free LRD. A UV spectrophotometer was used to analyze the supernatant solution at 243.5 nm (e.q., 1).[11]

$$EE = \frac{\text{Entrapped LRD}}{\text{Total LRD added}} X100 \quad \text{--- (1)}$$

In vitro release

The dialysis bag method was used to analyze the *in vitro* release pattern of the niosomal suspensions. The dialysis bags were cleaned in PBS and given a 24 hr soak time. In 2 mL of PBS, niosomal suspension (15.24 mg LRD equivalent) was diluted. The dialysis bag was then immersed in 20 mL of 20% isopropanol PBS and incubated for 24 hr at 37°C with 100 rpm. To maintain the sink condition throughout the experiment, 1 mL samples of the medium were taken at predefined intervals and then replaced with 1 mL of brand-new medium. UV spectrophotometer analysis was performed on the samples.[12]

Preparation of LRD-loaded niosomal patch

LN-14, LN-16, LN-18, and LN-19, the improved LRD niosome formulations, were created as transdermal patches.

LRD-filled niosomal patches were produced using the solvent evaporation method. The niosomal patches were made using different proportions of PG as a plasticizer and aqueous solutions of HPMC and/or Na-CMC. After using a magnetic stirrer to thoroughly homogenise the liquid, air bubbles were removed using sonication for 15 to 20 min. After that, the liquid was poured into glass molds and left to cure for 24 hr at room temperature (Table 2).[13,14]

Evaluation of patches

Drug excipient compatibility studies

The synergy between LRD with the excipients used in the investigation were examined using FTIR spectroscopy (Bruker) at a range of 4000-400 cm^{-1}.

Physical appearance

Each transdermal patches colour, clarity, flexibility, and smoothness were all visually examined. Three patches' thicknesses were measured using a micrometre (Mitutoyo Co., Japan), and a mean value was computed.[15]

Weight uniformity

Three patches for every formulation were chosen at random. After weighing 3 films from each batch individually, the average weight of the 3 films from each batch was determined.[16]

Folding Endurance

A film was folded in this experiment until it continuously broke in the same place. The number of folds a film can withstand at the same location without cracking or breaking is used to determine its folding endurance.[17]

Tensile strength

(40 x 15 mm) the film strip was used and it was attached an adhesive tape at one end in order to give the film support when it was placed inside the film holder. With a small pin sandwiched between the adhesive tapes, the other end of the film was kept straight while stretching. There was a tiny hole cut in the adhesive tape next to the pin where the hook was put. A thread was connected to this hook, passed over the pulley and a little pin was fastened to the other end to hold the weights in place. A tiny pointer on the thread moves across the graph paper that is attached to the baseplate. The tensile strength of the film was tested using a pulley system. Weights were slowly added to the pan in order to increase the pulling force. The weight needed to break the film served as a gauge for its breaking force.[18]

Moisture content

In desiccators containing calcium chloride, the prepared films are kept at room temperature for 24 hr. The films are weighed again at every specified interval until their weight is constant. Here is the formula to calculate the moisture content (e.q.2).[19]

$$\% \text{ Moisture content} = \frac{\text{Initial weight - Final weight}}{\text{Final weight}} X100 \quad \text{--- (2)}$$

Drug content analysis

One cm^2 of each patch was cut, and 100 mL of phosphate-buffered saline was added to the beaker. A magnetic bead was used to stir the medium. By using Whatman filter paper, the contents of the tube were filtered and the filtrate was spectrophotometrically analyzed for drug content at 243.5 nm against a control solution of no-drug films. The test was repeated to confirm the results.[20]

In vitro diffusion study

Franz diffusion cell receptor compartments with a capacity of 22 mL were used for the *in vitro* diffusion study. 22 mL of phosphate buffer, pH 7.4, was poured into the receiver compartment. In order to mount the cellophane membrane on the donor compartment, the transdermal patch was firmly pressed onto the centre of the cellophane membrane. Once this was done, the donor compartment was positioned so that the membrane surface just touched the surface of the receptor fluid. A water bath was used to keep the entire assembly at 32°C. Samples were

taken at different intervals and analyzed for drug content till 42 hr. During each time interval, equal volumes of buffer solution were added to the receptor phase.[12]

RESULTS

Results of chemical assessment

The particle size, zeta potential, % LRD content, EE, and the DR were as per Table 3.

The better formulation among the prepared niosomes (LN-1 to LN-25) LN-14, LN-16, LN-18, and LN-19 were fabricated in to transdermal patches and labelled them as LNP-14, LNP-16, LNP-18, and LNP-19 and were assessed for official tests for patches. The physical appearance of the LNP were very good. The thickness was ranged from 42.94±1.99 (LNP-16) to 46.28±3.65 (LNP-17). The weight of the LNP was least for LNP-18 (0.24±0.01) and more for LNP-16 (0.40±0.03). The LNP were flexible as the folding endurance was ranged from 118±1.00 to 124±1.00, this is least for LNP-14 and more for LNP-18. Similarly, the tensile strength of LNP were 81.81±6.63 to 89.33±3.19 g/cm^2. The moisture content in the prepared patches were within the limits

Table 2: Composition of LRD niosomal patches.

Formulation	HPMC (%w/w)	Na. CMC (%w/w)	PG (%w/w)	Propyl paraben	LRD niosomal dispersion (%w/w)
LNP-14	50	30	5	0.5	20
LNP-16	40	40	10	0.5	20
LNP-18	30	50	15	0.5	20
LNP-19	20	60	20	0.5	20

Table 3: Physicochemical assets of LN.

Formulation	Particle size (µm)	Zeta potential (mV)	% LRD content	EE (%)	DR (%)
LN-1	27.5±2.36	-85.3±0.02	89.58±1.25	85.29±1.84	89.22±2.81
LN-2	29.6±1.02	-56.6±1.03	95.62±2.36	89.65±3.64	91.25±5.15
LN-3	30.2±1.54	-61.0±2.03	88.29±3.05	90.37±2.55	98.23±2.99
LN-4	28.6±3.12	-58.7±1.05	92.34±1.85	84.17±1.64	92.35±6.25
LN-5	24.1±0.62	-64.8±1.31	93.16±1.65	88.45±1.90	92.66±3.62
LN-6	36.2±0.85	-78.8±2.31	90.15±2.84	89.38±2.08	92.00±4.51
LN-7	42.1±0.69	-71.0±0.51	88.27±1.95	90.78±3.62	96.31±0.84
LN-8	48.5±1.02	-53.8±0.14	89.97±2.65	91.27±3.44	96.87±5.66
LN-9	19.2±0.99	-80.1±1.64	91.28±4.24	88.46±1.95	91.28±2.98
LN-10	24.9±1.31	-60.3±1.82	90.28±6.32	85.56±6.44	91.23±3.87
LN-11	26.8±0.51	-71.2±2.15	92.48±2.84	89.39±6.49	95.16±4.14
LN-12	34.1±0.54	-55.2±3.02	93.87±3.99	90.37±2.84	92.02±2.07
LN-13	39.2±1.08	-59.9±1.84	94.18±6.48	91.28±4.51	90.07±3.19
LN-14	45.2±1.33	-73.2±1.64	93.88±5.65	92.36±6.26	97.84±5.02
LN-15	18.9±0.14	-55.3±2.54	92.36±4.44	89.97±4.52	90.26±4.00
LN-16	16.7±0.87	-60.4±1.75	95.61±3.88	93.85±3.48	98.58±2.31
LN-17	33.5±0.22	-82.7±1.69	90.28±5.95	90.79±6.29	92.65±6.66
LN-18	40.1±0.05	-66.6±2.17	91.29±4.11	91.46±5.28	93.31±2.17
LN-19	27.4±0.07	-69.2±3.12	89.25±2.02	92.68±3.48	93.65±3.85
LN-20	30.2±1.04	-57.0±0.64	93.26±3.30	91.65±6.25	92.88±2.99
LN-21	19.0±1.30	-82.8±2.00	94.07±2.85	93.65±2.84	88.26±2.64
LN-22	23.7±2.02	-84.4±1.34	90.12±6.44	90.86±3.63	95.51±3.45
LN-23	44.4±1.07	-55.3±2.99	91.23±2.28	88.81±1.52	93.19±3.78
LN-24	19.5±0.08	-57.6±3.45	88.92±3.19	85.26±3.02	98.24±1.98
LN-25	31.3±2.31	-66.7±3.25	89.21±6.25	88.91±2.02	93.28±2.45

Values in mean ± SD; *n*=3.

Table 4: Physicochemical of LNP.

Formulation	Physical appearance	Thickness (mm)	Uniformity of weight (mg)	Folding endurance	Tensile strength (g/cm²)	Moisture content (%)	Assay (%)
LNP-14	Very good	42.94±1.99	0.35±0.02	118±1.00	81.81±6.63	3.84±0.21	97.16±3.45
LNP-16	Good	46.28±3.65	0.40±0.03	123±2.08	87.17±4.05	2.65±0.15	95.39±1.28
LNP-18	Very good	45.37±2.08	0.24±0.01	124±1.00	89.33±3.19	4.17±0.09	98.00±4.49
LNP-19	Good	44.00±0.15	0.39±0.02	119±4.35	83.62±2.01	2.98±0.11	97.18±3.88

Values in mean ± SD; *n*=3.

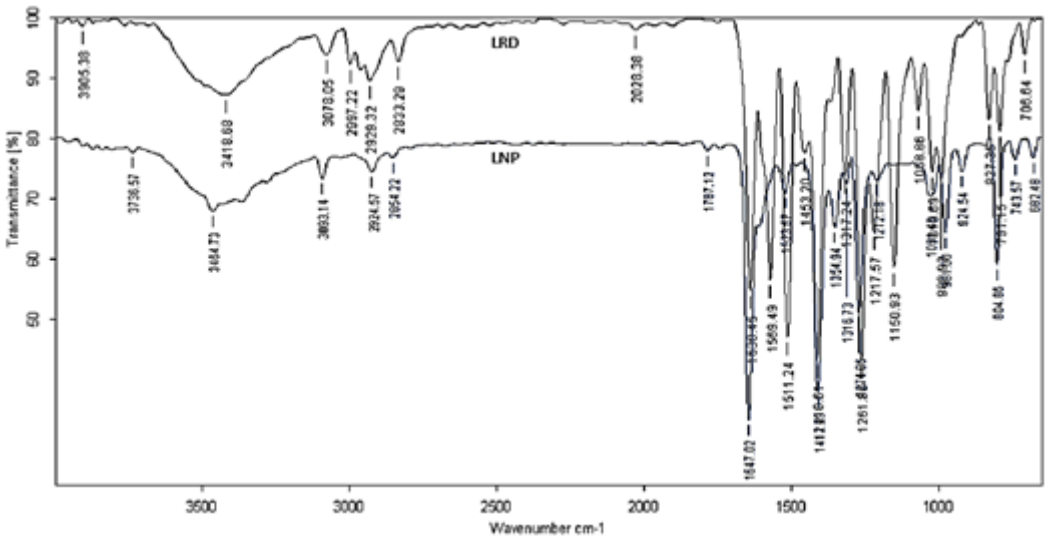

Figure 1: FTIR spectrum of the LRD and the formulation (LNP).

(<4%) and the LRD content was 95.39±1.28 to 98.00±4.49% (Table 4).

Compatibility studies

Figure 1 displays the FTIR spectra of the LN and LRD.

Physical examination of the LNP

The LNP was visually inspected and found to be clear, transparent, and homogeneous with no lumps, clumps, or precipitates. Since the pH range of LN is similar to that of skin, they can be used in dermatology procedures without causing skin irritation.

Optimization of the LNP

According to BBD research, cholesterol, span-40, span-60, and span-80 concentrations significantly affect *in vitro* LRD discharge. The outcomes of 25 runs and the responses of the created LN were shown in Table 2. According to Figures 2 and 3, these 3D plots represent how different factors interact to affect responses as well as how different factors affect a response simultaneously.

Response (Y1): effect of independent variables on % DR of LRD

The model is suggested to be significant by the model's F-value of 15.45. The final equation in terms of coded factors is as follows.

$$DR = +93.28 - 0.5958A + 3.21B + 0.1167C + 1.74D - 1.98AB - 0.3575AC - 0.7725AD + 0.1375BC - 0.5500BD + 0.3050CD - 0.9454A^2 + 0.2758B^2 + 0.7858C^2 + 0.2421D^2$$

In vitro drug discharge

The LNP underwent a 42 hr *in vitro* LRD discharge trial. The LNP (LN-16) demonstrated a more controlled but gradually increasing discharge of LRD 40–50% at the 6th hr of study at pH 6 and at the 42 hr of study design compared to the control (Figure 4).

DISCUSSION

The particle size of the niosomes was uniform and ranged from 18.9±0.14 µm (LN-15) to 48.5±1.02µm (LN-8). The zeta potential ranged from -53.8±0.14 mV (LN-8) to -85.3±0.02 mV (LN-1). The LRD content ranged from 88.29±3.05 (LN-3) to 95.61±3.88 (LN-16), while the EE% ranged from 84.17±1.64 (LN-4) to

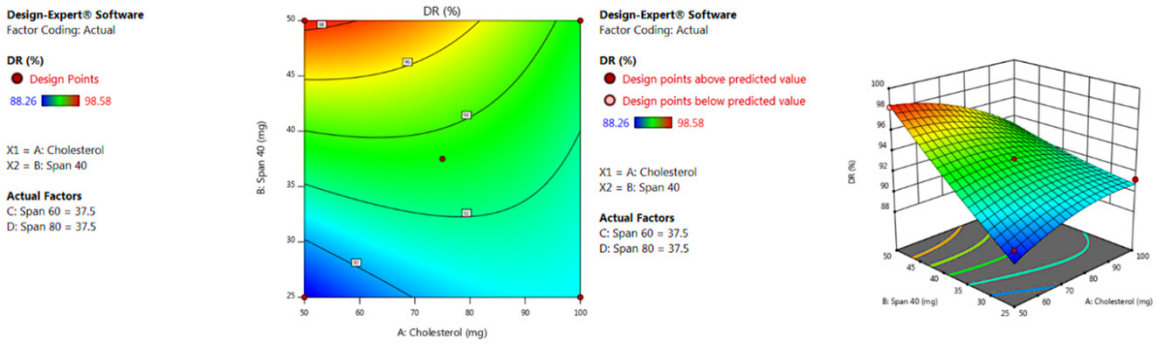

Figure 2: (a) Optimized LNP (LN-16) 3D Surface plot of % LRD discharge response at y = pH 7.4; (b). Optimized LNP (LN-16) interaction diagram.

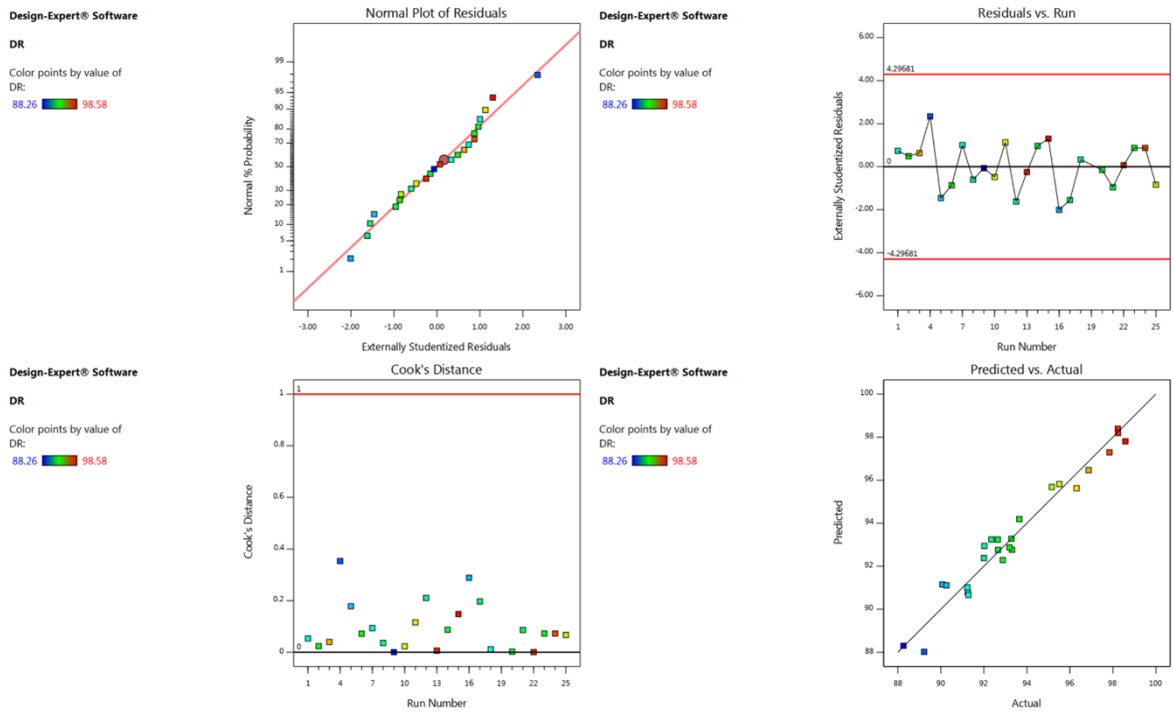

Figure 3: Actual and expected values as linear correlation plots and the associated residual plots for various responses.

93.85±3.48% (LN-16). The LRD discharge was least in LN-21 (88.26±2.64%) and efficient for LN-16 (98.58±2.31) (Table 3).

The physicochemical assets of the prepared patches were as per Table 4 indicating good appeal, uniform thickness/weight, flexibility that were confirmed by appreciable folding endurance and tensile strength.

The FTIR spectra revealed that the characteristic peaks and stretches present in the LRD are observed undisturbed even in the spectra of the formulation indicating the compatibility of LRD with the excipients used.

Visual inspection revealed the LNP to be homogenous, clean, and transparent with no lumps, clumps, or precipitates. LN can be used in dermatological operations without irritating the skin since its pH range is comparable to that of skin.

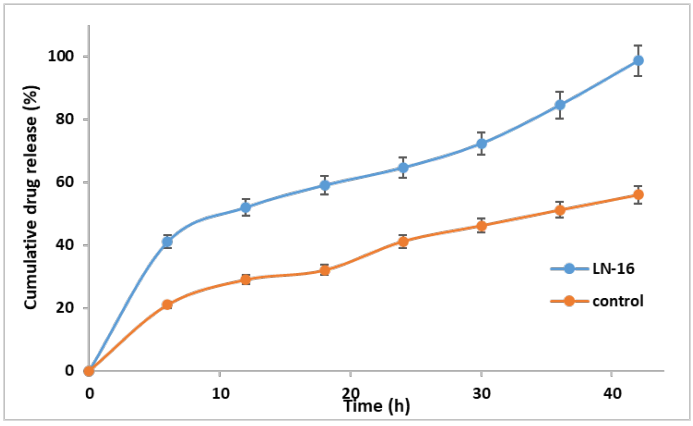

Figure 4: *In vitro* discharge (%) of LNP vs. control at pH 6.

According to BBD research, cholesterol, span-40, span-60, and span-80 concentrations significantly affect *in vitro* LRD discharge. The model is suggested to be significant by the model's *F*-value

of 15.45. An F-value this large might happen to owe to noise only 0.01% of the time. Model terms are considered significant if their *p*-values are less than 0.05. B, D, and AB are important model terms in this situation. Model terms are not significant if the value is higher than 0.10. Model reduction may enhance the model if there are numerous unimportant model terms (except those necessary to support hierarchy). The signal-to-noise ratio is a measurement of model precision. An ideal ratio is > 4. A sufficient signal is indicated by the ratio of 14.019. To move around the design space, utilize this model.

The LNP when tested for *in vitro* LRD discharge for 42 hr. The LNP (LN-16) demonstrated a more controlled but gradually increasing discharge of LRD than the control patch (containing non Niosomal drug in the patch). LRD discharge from optimized LNP was studied for 42 hr using the linear regression equation $Y = mx + b$ and r^2 at pH 6, i.e., values for LRD, $Y = 1.9329x + 18.408$ and $r^2 = 0.8995$ compared to the control ($1.198x + 9.4167$ and $r^2 = 0.9306$) (Figure 4).

CONCLUSION

Successful preparation and incorporation of LRD-loaded niosomal nanovesicles into a skin patch for transdermal delivery. It's interesting that the formulation (LN-16) with 75:50:50:37.5 mg of CHL: Span 40: Span 60: Span 80 had a considerably greater encapsulation efficiency than the formulations with other ratios. The transdermal administration of LRD was greatly improved by the niosomal patches, which had a significantly greater permeability coefficient of LRD than the standard patch. From the aforementioned results, it can be inferred that niosome-based patches that mediate TDD are a potential method for avoiding the unpleasant taste of the oral liquid dosage form of LRD, reducing GIT-related side effects, and extending LRD's presence in the systemic circulation, thereby allowing for less frequent dosing. In conclusion, niosome-based transdermal patches might be an effective way to treat class II medications and medications with GIT-related adverse effects.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

LRD: Loratadine; **BPS-II:** Biopharmaceutical Classification System; **DOE:** Design of experiments; **PBS:** Phosphate Buffer Solution; **HPLC:** High Performance Liquid Chromatography; **rpm:** rotations per minute; **LN:** Loratadine niosomes; **DCP:** Dicetyl phosphate; **PS:** Particle size; **ZP:** Zeta Potential; **ELS:** Electrophoretic light scattering; **EE:** Entrapment efficiency: **LNP:** Loratadine Nisomal Patch; **HPMC:** Hydroxy Propyl Methyl cellulose; **Na CMC:** Sodium Carboxy methyl cellulose; **BBD:** Box Behnken Design.

SUMMARY

Niosomes that had been loaded with LRD were processed, and the best ones were turned into patches for transdermal distribution. The CHL was used to make the niosomes: employing BBD, span 40, span 60, and span 80 in different ratios. Niosome-based patches outperformed non-neosomal LRD patches in terms of release and penetration when they were evaluated for their physicochemical qualities. In conclusion, niosome-based transdermal patches may be a successful strategy to treat class II drugs and drugs having harmful effects on the GIT.

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