

Research Article

# Loratadine-loaded Niosomal Transdermal Patch for Treating Allergic Issues: A Design Expert's Associated Fabrication and Evaluation

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## I N F O

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## A B S T R A C T

**Introduction:** Loratadine (LRD) is a second-generation H1 histamine antagonist and is helpful in the treatment of allergies.

**Methods:** The Box Behnken design (BBD) was used in this study to create nine LRD niosomes, which were then cast in solvent and put on transdermal patches. The niosomes' dimensions, shape, zeta potential, and degree of entrapment efficiency were then assessed. On the LRD entrapment, the niosomes' cholesterol, Span-40, Span-60, and Span-80 concentrations were measured. The patch system was filled with the optimised niosomal formulations. Then, each patch was described using its physicochemical properties and results from in vitro permeation studies.

**Results:** Patches containing niosomal vesicles, in contrast to control patches, demonstrated improved drug release. It was shown that niosomal patches exhibited greater penetration than control patches. Niosomes' surfactant serves as a permeation enhancer and enhances LRD permeation from niosomes.

**Conclusion:** The study concluded that the niosome-based transdermal patches might effectively distribute LRD medications trans-dermally while minimising GIT adverse effects.

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

## Introduction

Transdermal medication administration is superior to traditional drug delivery because it avoids first-pass liver metabolism and increases patient comfort and compliance.<sup>1</sup> There has been much research on the transdermal method of niosomal medication delivery.<sup>2</sup>

Loratadine (LRD) is a second-generation H1 histamine

antagonist and is helpful in the treatment of allergies. On examining the structure, it is found to be closely related to tricyclic antidepressants like imipramine and distantly related to the atypical antipsychotic quetiapine. It is a medication of the BPS-II family, and improving its solubility is necessary for both absorption and bioavailability.<sup>3</sup>

It has been investigated if niosomes might serve as platforms for the transdermal, cutaneous, and oral administration

of drugs. The ability of niosomes to entrap hydrophilic, lipophilic, and amphiphilic substances is extraordinary (in terms of affordability and ease of formulation). One of the most advanced pharmaceutical dosage techniques for swiftly transporting medications from the skin to the bloodstream is transdermal patches. They distribute drugs in a time-limited, modified, and regulated manner, at a pre-decided pace.<sup>4,5</sup>

Due to its statically manipulable nature and the fact that only one variable can be studied at a time, traditional research approaches typically examine the influence of one variable at a time. Combining these two variables may yield inaccurate results due to their interdependence. Multivariate analysis necessitates the use of a Design of Experiments (DOE) approach, which often implies that only specific elements are encompassed by the agreement. The authors tested the percentage of LRD release in response to polymer concentration using Design Expert (V.11) software.<sup>6</sup>

## Material and Methods

### Materials

Loratadine was given by Cipla Ltd. in Bengaluru. Merck provided the following ingredients: cholesterol, Span 40/60/80, dichloromethane, and dicetyl phosphate. Double-distilled water and a buffer (pH 6 and 7.4, respectively) were created in the lab.

### Saturation Solubility of LRD

Both the saturation solubility of LRD in PBS with a pH of 7.4 and PBS with 20% isopropyl alcohol were examined at 37 °C. Extra LRD was added to a 25 ml beaker containing 10 ml of each solvent. In a shaker incubator, the beakers were firmly covered and agitated at 100 rpm and 37 °C for 24 hours.<sup>7</sup> 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.

### Preparation of the LRD Niosomes

The production of Loratadine niosomes (LN) (25 formulations) included the ether injection method. Dichloromethane was utilised to dissolve the cholesterol; Span-40, Span-60, and Span-80 were then mixed with methanol (4 ml) containing a specific quantity of LRD which was then dissolved in 16 ml of diethyl ether. The mixture was then supplemented with dicetyl phosphate (DCP) as required. The generated solution was then slowly injected at a rate of 1 ml/min with a syringe pump into PBS (20 ml) having a pH of 7.4. A magnetic stirrer was used to continuously stir the solution while keeping it at a temperature of 60–65 °C. Niosomes were created as a result of evaporation that was triggered by temperature differences between the phases (Table 1).<sup>8</sup>

**Table 1. Various Formulations of Loratadine Niosomes**

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.

LRD: Loratadine; LN: Loratadine niosomes; DCM: Dichloromethane; PBS: Phosphate Buffer Solution; q.s.: Quantity sufficient

### Purification of Drug-loaded Niosomes

Using a dialysis membrane approach, drug-loaded niosomes were purified to remove the free drug from the niosomal solution. To achieve this, the HiMedia dialysis membrane was thoroughly moistened by soaking it in saline solution for two hours prior to dialysis. 200 cc of phosphate buffer (pH 7.4) was added after niosomal vesicles that had been loaded with LRD were put in a dialysis bag. A magnetic stirrer was used to agitate the receiver medium at 500 revolutions per minute (15.24 g). At regular intervals, 5 ml of the sample was removed and replaced with an equivalent volume of fresh medium. The quantity of free drug was then calculated using spectrophotometric analysis. By using a statistical paired t-test with a 5% threshold of significance, purification time was shortened.<sup>9</sup>

### Evaluation

The prepared LN were assessed for the following constraints:

#### Particle Size (PS) and Zeta Potential (ZP)

According to the Zetasizer nano user manual (Man0485-1.1), niosome PS and ZP were evaluated. Three separate experiments' results were calculated in the form of mean and standard deviation. In order to determine the ZP of the niosomes, the surface charge of the particles was discovered using electrophoretic light scattering (ELS). To create a translucent solution, the niosomes were dissolved in distilled water and sonicated at 25 °C. The data were presented in the form of mean and SD after running every experiment thrice.<sup>10</sup>

#### LRD Entrapment Efficiency (EE)

Free LRD is always present in the LN since the complete LRD has never been contained by a dispersion (LN). To separate

the free LRD, 0.1 g of LN was soaked in 10 ml of PBS (pH 7.4) and subjected to a 10 min bath sonication process. To get rid of the free LRD, the supernatant solution from centrifuging the LN at 10,000 rpm for 30 min at 25 ± 0.1 °C was filtered. The supernatant solution was examined using a UV spectrophotometer at 243.5 nm equation 1.<sup>11</sup>

$$EE = \frac{\text{Entrapped LRD}}{\text{Total LRD added}} \times 100 \quad (1)$$

### In Vitro Release

The in vitro release pattern of the niosomal suspensions was investigated using the dialysis bag technique. The dialysis bags were cleaned using PBS and were left to soak for 24 hours. Niosomal suspension (15.24 mg LRD equivalent) was diluted in 2 ml of PBS. Incubation was carried out at 37 °C for 24 hours at 100 rpm after submerging the dialysis bag in PBS (20 ml) containing 20% isopropanol. At predetermined intervals, 1 ml samples of the medium were obtained and subsequently swapped out with 1 ml of fresh media to maintain the sink condition during the experiment. The samples were subjected to examination using a UV spectrophotometer.<sup>12</sup>

### 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.

The solvent evaporation technique was used to create niosomal patches loaded with LRD. The niosomal patches were created utilising PG as a plasticiser in various ratios together with aqueous solutions of HPMC and/ or Na-CMC. After fully homogenising the liquid using a magnetic stirrer, air bubbles were eliminated using sonication for 15 to 20 minutes. The liquid was then put into glass moulds and let to sit at room temperature for 24 hours to cure (Table 2).<sup>13,14</sup>

Table 2. Composition of LRD Niosomal Patches

Formulation	HPMC (%w/w)	Na.CMC (%w/w)	PG (%w/w)	Propyl Paraben (mg)	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

LNP: Loratadine Niosomal Patch; HPMC: Hydroxy propyl methyl cellulose; Na. CMC: Sodium carboxymethyl cellulose; PG: Propylene glycol; LRD: Loratadine

## Evaluation of Patches

### Drug Excipient Compatibility Studies

The synergy between LRD and the excipients used (transdermal patch) was examined using FTIR spectroscopy (Bruker) at a range of 4000–400 cm<sup>-1</sup>.

### Physical Appearance

Each transdermal patch's colour, clarity, flexibility, and smoothness were visually examined. Three patches' thicknesses were measured using a micrometre (Mitutoyo Co., Japan), and a mean value was computed.<sup>15</sup>

### Weight Uniformity

For each formulation, three patches were randomly selected. The average weight of the three films from each batch was calculated after weighing the individual three films from each batch.<sup>16</sup>

### Folding Endurance

In this experiment, a film was folded until it consistently broke in the same spot. A film's folding endurance is measured by the number of folds it can endure in the same area without breaking or cracking.<sup>17</sup>

### Tensile Strength

The utilised film strip (40 x 15 mm) had an adhesive tape affixed to one end to stabilise the film when it was inserted into the film holder. The other end of the film was held straight during stretching with a tiny pin inserted between the adhesive tapes. The adhesive tape had a small hole drilled into it just close to the pin where the hook was placed. To secure the weights, a thread was attached to this hook, passed over the pulley, and a small pin was attached to the other end. The graph paper attached to the baseplate was moved across by a little pointer on the thread. The tensile strength of the film was tested using a pulley system. The pulling force was increased by slowly adding weights to the pan. The weight needed to break the film served as a gauge for its breaking force.<sup>18</sup>

### Moisture Content

The prepared films were kept at room temperature for 24 hours in desiccators containing calcium chloride. The

weight of films is measured at every specified interval until their weight is constant. Here is the formula to calculate the moisture content equation 2.<sup>19</sup>

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100 \quad (2)$$

### Drug Content Analysis

100 ml of phosphate-buffered saline was added to the beaker after each patch had its surface area trimmed to one cm<sup>2</sup>. The medium was moved around with a magnetic bead. The tube's contents were filtered using Whatman filter paper, and the filtrate was then spectrophotometrically examined for drug content at 243.5 nm in comparison to a solution of no-drug films as a control. The examination was repeated to verify the findings.<sup>20</sup>

### In Vitro Diffusion Study

For the in vitro diffusion research, Franz diffusion cell receptor compartments with a 22 ml capacity were employed. 22 ml of pH 7.4 phosphate buffer was placed into the receiver chamber. The transdermal patch was firmly pushed into the cellophane membrane's core in order to place it on the donor compartment. The donor compartment was then positioned so that the membrane surface barely brushed the receptor fluid's surface. The entire assembly was maintained at 32 °C by means of a water bath. Samples were collected at various intervals, and they were examined for drug content over 42 hours. Equal amounts of buffer solution were introduced to the receptor phase at each interval.

## Results and Discussion

### Results of Chemical Assessment

The particle size of the niosomes was uniform and ranged from 18.9 ± 0.14 μm (LN-15) to 48.5 ± 1.02 μm (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 (LN-9) to 95.61 ± 3.88 (LN-16), while the EE% ranged from 88.46 ± 5.16 (LN-9) to 92.00 ± 0.92 % (LN-16). The LRD discharge was least in LN-21 (88.26 ± 2.64%) and was efficient for LN-16 (98.58 ± 2.31). LRD content was more in LN-16 (99.15 ± 3.45%) and least in LN-21 (90.21 ± 5.16%) (Table 3).

**Table 3. Physicochemical Assets of LN**

Formulation	Particle Size (μm)	Zeta Potential (mV)	% LRD Content	EE (%)	DR (%)	Drug Content (%)
LN-1	27.5 ± 2.36	-85.3 ± 0.02	89.58 ± 1.25	88.60 ± 1.85	89.22 ± 2.81	94.12 ± 2.03
LN-2	29.6 ± 1.02	-56.6 ± 1.03	95.62 ± 2.36	89.65 ± 1.64	91.25 ± 5.15	95.24 ± 5.85
LN-3	30.2 ± 1.54	-61.0 ± 2.03	88.29 ± 3.05	90.37 ± 3.80	98.23 ± 2.99	93.08 ± 6.45
LN-4	28.6 ± 3.12	-58.7 ± 1.05	92.34 ± 1.85	91.00 ± 2.08	92.35 ± 6.25	97.15 ± 1.08

LN-5	24.1 ± 0.62	-64.8 ± 1.31	93.16 ± 1.65	90.37 ± 1.65	92.66 ± 3.62	95.46 ± 5.55
LN-6	36.2 ± 0.85	-78.8 ± 2.31	90.15 ± 2.84	89.38 ± 2.22	92.00 ± 4.51	98.54 ± 4.24
LN-7	42.1 ± 0.69	-71.0 ± 0.51	88.27 ± 1.95	90.78 ± 3.38	96.31 ± 0.84	92.38 ± 7.18
LN-8	48.5 ± 1.02	-53.8 ± 0.14	89.97 ± 2.65	91.27 ± 0.96	96.87 ± 5.66	90.45 ± 3.15
LN-9	19.2 ± 0.99	-80.1 ± 1.64	91.28 ± 4.24	88.46 ± 5.16	91.28 ± 2.98	91.08 ± 2.75
LN-10	24.9 ± 1.31	-60.3 ± 1.82	90.28 ± 6.32	89.99 ± 4.05	91.23 ± 3.87	96.78 ± 4.21
LN-11	26.8 ± 0.51	-71.2 ± 2.15	92.48 ± 2.84	89.39 ± 7.15	95.16 ± 4.14	94.62 ± 3.96
LN-12	34.1 ± 0.54	-55.2 ± 3.02	93.87 ± 3.99	90.37 ± 2.65	92.02 ± 2.07	96.38 ± 5.33
LN-13	39.2 ± 1.08	-59.9 ± 1.84	94.18 ± 6.48	91.28 ± 3.25	90.07 ± 3.19	97.84 ± 3.28
LN-14	45.2 ± 1.33	-73.2 ± 1.64	93.88 ± 5.65	91.41 ± 4.98	97.84 ± 5.02	98.62 ± 1.95
LN-15	18.9 ± 0.14	-55.3 ± 2.54	92.36 ± 4.44	89.97 ± 1.74	90.26 ± 4.00	95.68 ± 1.65
LN-16	16.7 ± 0.87	-60.4 ± 1.75	95.61 ± 3.88	92.00 ± 0.92	98.58 ± 2.31	99.15 ± 3.45
LN-17	33.5 ± 0.22	-82.7 ± 1.69	90.28 ± 5.95	90.79 ± 1.05	92.65 ± 6.66	96.37 ± 2.70
LN-18	40.1 ± 0.05	-66.6 ± 2.17	91.29 ± 4.11	91.46 ± 2.05	93.31 ± 2.17	97.18 ± 2.05
LN-19	27.4 ± 0.07	-69.2 ± 3.12	89.25 ± 2.02	90.55 ± 6.87	93.65 ± 3.85	95.44 ± 3.33
LN-20	30.2 ± 1.04	-57.0 ± 0.64	93.26 ± 3.30	91.65 ± 5.02	92.88 ± 2.99	96.56 ± 4.64
LN-21	19.0 ± 1.30	-82.8 ± 2.00	94.07 ± 2.85	89.10 ± 4.52	88.26 ± 2.64	90.21 ± 5.16
LN-22	23.7 ± 2.02	-84.4 ± 1.34	90.12 ± 6.44	89.30 ± 6.58	95.51 ± 3.45	93.65 ± 4.89
LN-23	44.4 ± 1.07	-55.3 ± 2.99	91.23 ± 2.28	88.81 ± 3.52	93.19 ± 3.78	94.68 ± 2.92
LN-24	19.5 ± 0.08	-57.6 ± 3.45	88.92 ± 3.19	91.00 ± 0.39	98.24 ± 1.98	96.48 ± 3.91
LN-25	31.3 ± 2.31	-66.7 ± 3.25	89.21 ± 6.25	88.91 ± 1.25	93.28 ± 2.45	90.84 ± 1.46

Values in mean ± SD; n = 3; LN: Loratadine Niosomes; LRD: Loratadine; EE: Entrapment efficiency; DR: Drug release

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

**Table 4. Physicochemical Properties of LNP**

Formulation	Physical Appearance	Thickness (mm)	Uniformity of Weight (mg)	Folding Endurance	Tensile Strength (g/cm <sup>2</sup> )	Moisture Content (%)	Assay (%)
LNP-14	Very good	42.94 ± 1.99	0.35 ± 0.02	118 ± 1.00	91.81 ± 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	85.33 ± 3.19	4.17 ± 0.09	98.00 ± 4.49
LNP-19	Good	44.00 ± 0.15	0.39 ± 0.02	119 ± 4.35	88.62 ± 2.01	2.98 ± 0.11	97.18 ± 3.88
Values in mean ± SD; n = 3							

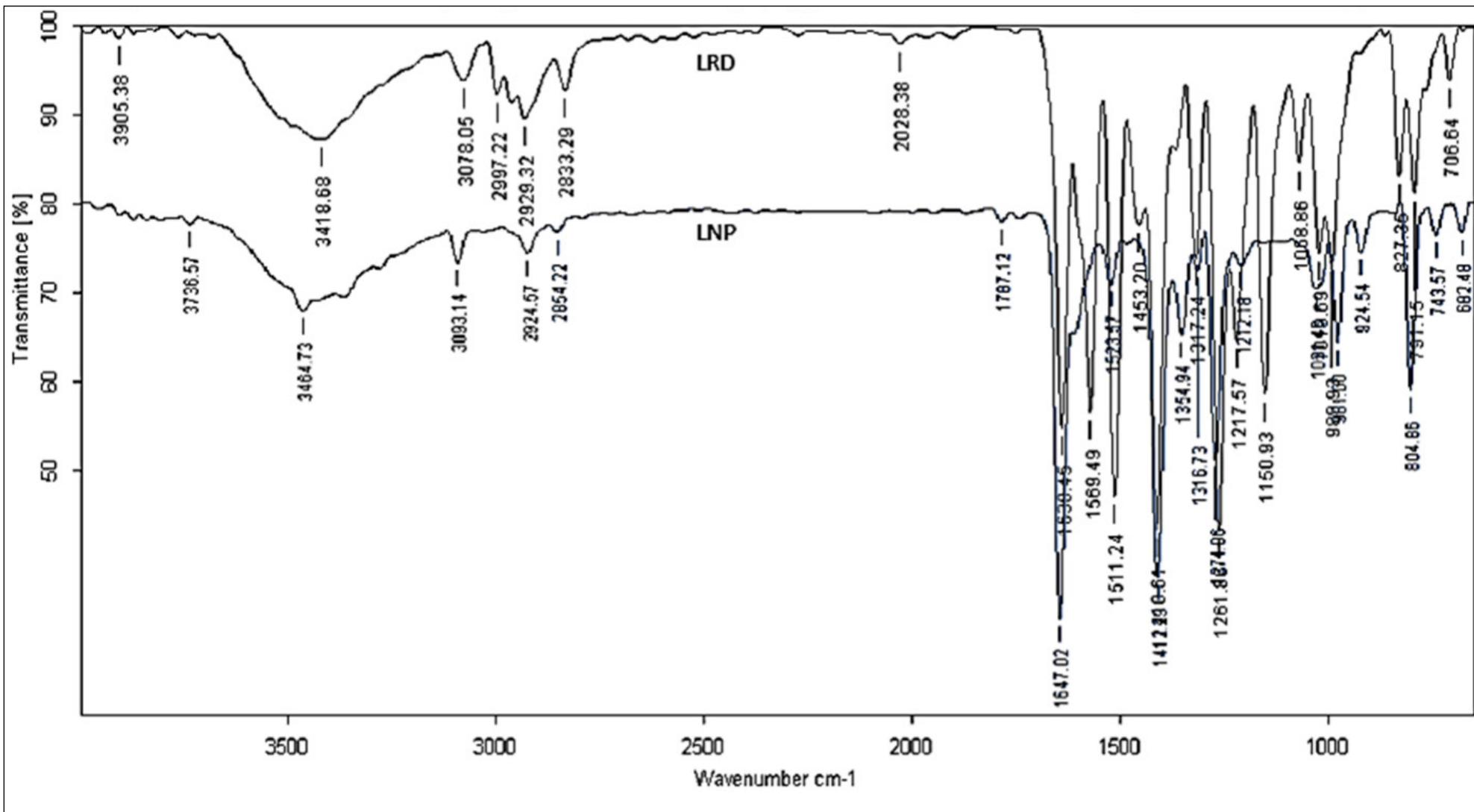


Figure 1. FTIR Spectrum of the LRD and the Formulation (LNP)

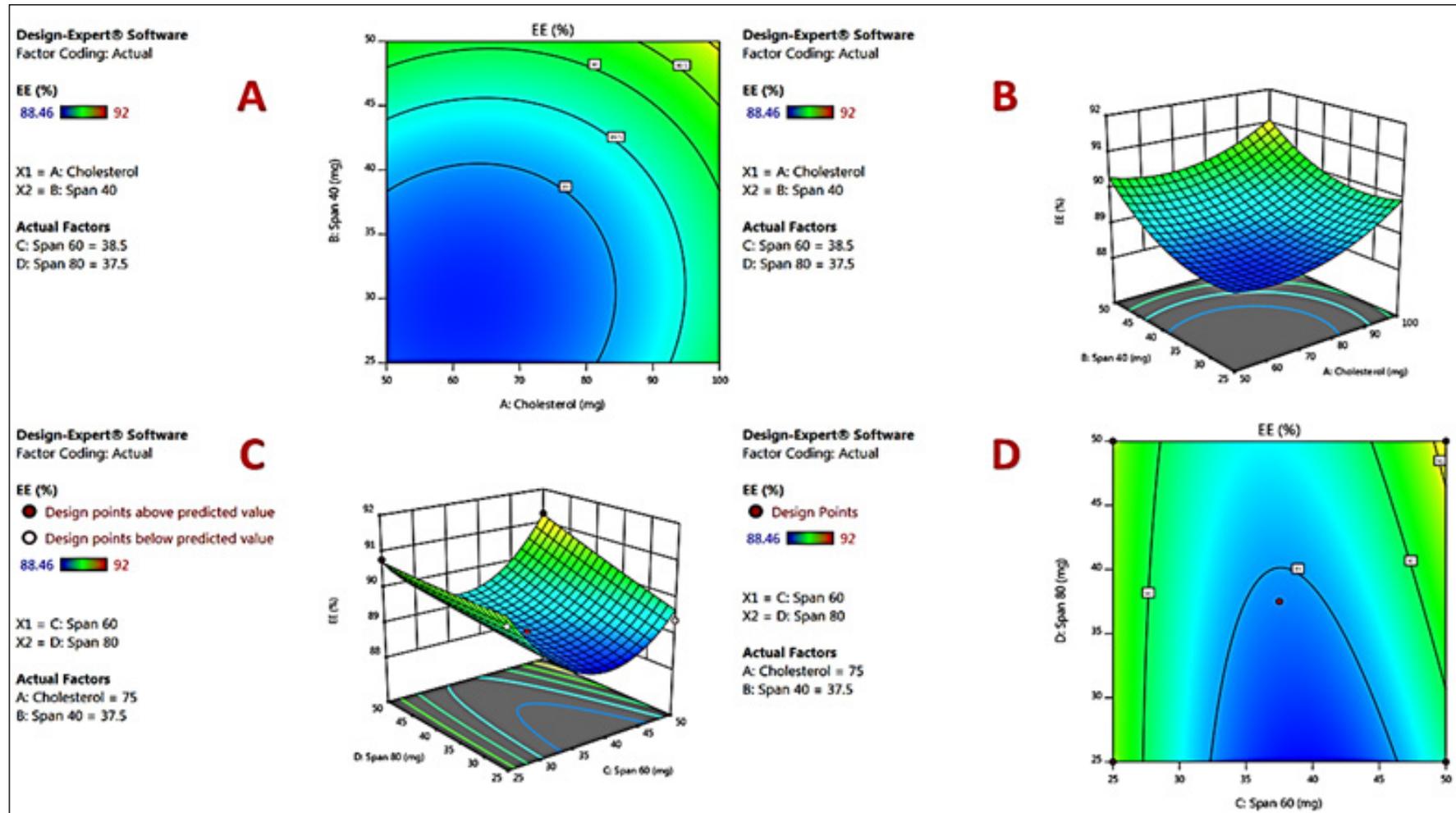


Figure 2(A).2D Plot Showing the Impact of Cholesterol and Span-40 on LRD Entrapment  
(B).3D Plot Showing the Impact of Cholesterol and Span-40 on LRD Entrapment  
(C).2D Plot Showing the Impact of Span-60 and Span-80 on LRD Entrapment  
(D).3D Plot Showing the Impact of Span-60 and Span-80 on LRD Entrapment

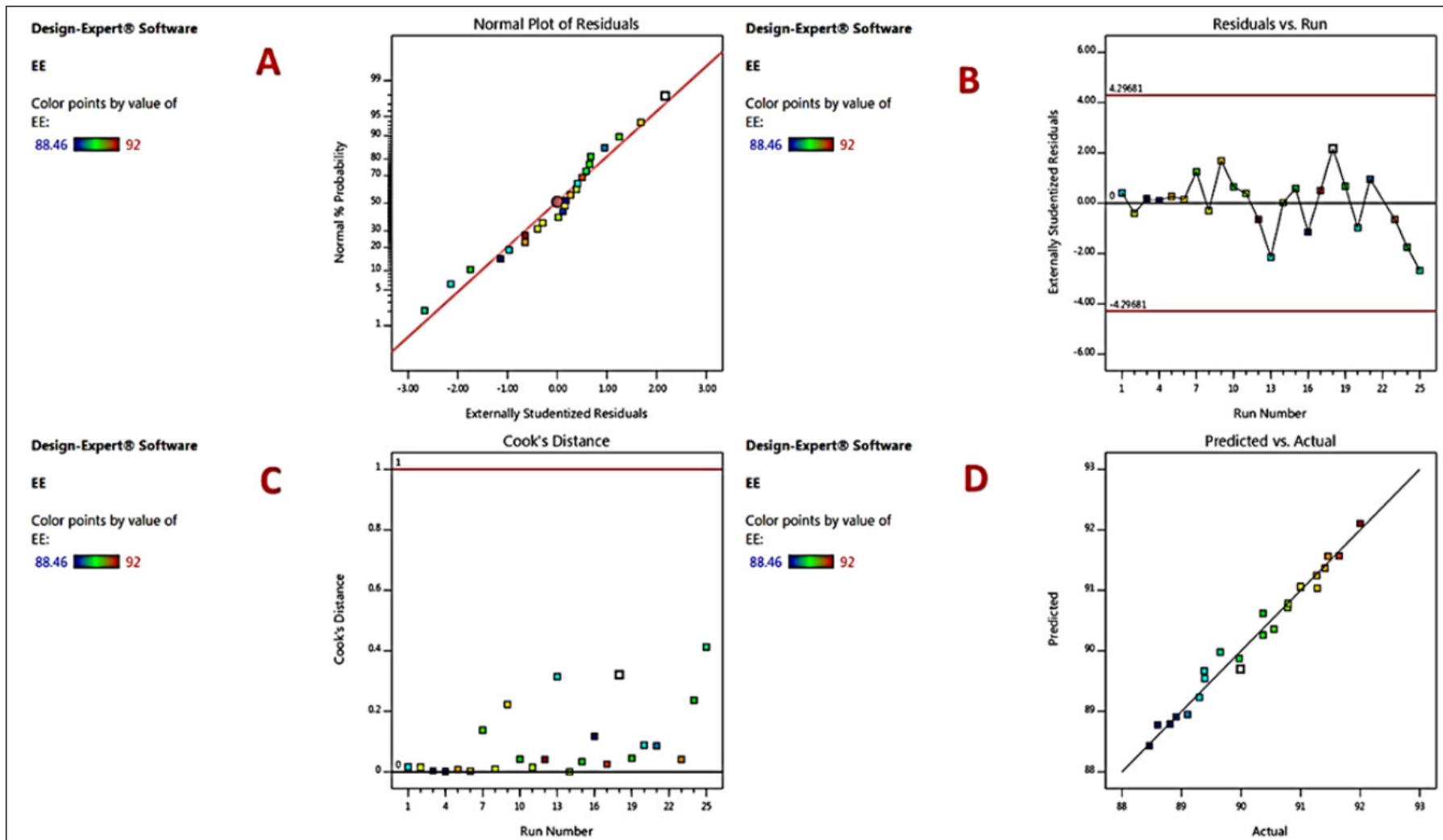


Figure 3. Actual and Expected Values as Linear Correlation Plots and the Associated Residual Plots for Various Responses

## Compatibility Studies

Figure 1 displays the FTIR spectra of the LN and LRD. The characteristic peaks and stretches present in the LRD are observed undisturbed even in the spectra of the formulation.

## Physical Examination of the LNP

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. The particle size study included a range of 0.3–5.0  $\mu\text{m}$ .

## Optimisation 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 have been shown in Table 3. The 3D plots in Figures 2 and 3 are well-known for helping researchers understand how different factors interact to affect responses as well as how different factors affect a response simultaneously.

## Response (YI): Effect of Independent Variables on % EE of LRD

The model's F value of 30.52 suggested that only 0.01% of the time could an F value this large be due to noise. If a model term's p value is under 0.05, it is deemed significant. In this context, key model terms include B, D, and AB. If the value is more than 0.10, model terms are not meaningful. If the model has a large number of irrelevant terms (apart from those required to maintain hierarchy), model reduction may improve the model.

$$EE = + 88.91 + 0.4967A + 0.6392B - 0.1058C + 0.4183D - 0.1050AB + 0.1075 AC - 0.1375AD + 0.4750BC + 0.4975BD + 0.3700CD + 0.5404A^2 + 0.5667B^2 + 1.62C^2 + 0.0329D^2$$

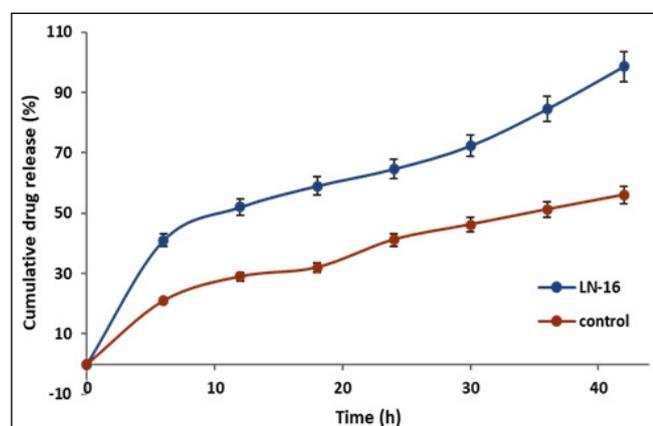


Figure 4. In Vitro Discharge (%) of LNP vs Control at pH 6

The signal-to-noise ratio is a measurement of model precision. An ideal ratio is greater than 4. A sufficient signal is indicated by a ratio of 19.529. To move around the design space, this model should be utilised.

## In Vitro Drug Discharge

A 42-hour in vitro LRD discharge test was performed on the LNP. At the 6th hour of the study at pH 6 and at the 42nd hour of the study design, the LNP (LN-16) showed a more controlled but gradually increasing discharge of LRD 40–50%. Every LNP exhibited sustained and ongoing discharge behaviour. The linear regression equation  $Y = mx + b$  and  $r^2$  at pH 6 were used to study LRD discharge from the optimised LNP over 42 hours, yielding results for the LRD of  $Y = 1.9329x + 18.408$  and  $r^2 = 0.8995$  in comparison to the control of  $1.198x + 9.4167$  and  $r^2 = 0.9306$  (Figure 4).

## Conclusion

Niosomes surfactant serves as a permeation enhancer and enhances LRD permeation from niosomes. Niosome-based transdermal patches might effectively distribute LRD medications trans-dermally while minimising GIT adverse effects.

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Conflict of Interest: None

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