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Optimization and Characterization of Niosomal Transdermal Patch of Lornoxicam

Azimullah Wafa[1], Sudhakar CK[2], Nagina Belali[3], Roshaan Raihan[4], Swati Tyagi[5]

[1,3,4]Kabul University, Faculty of Pharmacy, Department of Pharmaceutics

[2]Lovely Institute of Technology (Pharmacy) School of Pharmaceutical Sciences Lovely Professional University, Phagwara, Punjab

[5]Raj Kumar Goel Institute of Technology, Ghaziabad, India

✉E-mail: azimullah1984@gmail.com **(**Corresponding Author)

ABSTRACT

Lornoxicam has a low solubility; therefore, its oral use is restricted due to its adverse effects on the gastric system. Hence, we intend to design a niosomal transdermal patch of Lornoxicam to improve clinical efficacy and enhance its absorption and penetration through the skin by applying surfactants. Surfactants generally improve the solubility and penetration of the active ingredients. The niosome vesicles are prepared by using the rotary film evaporation technique. The result showed that the percentage entrapment efficacy of unsonicated niosome vesicles was 70.13 ±0.2% and sonicated 72.39 ±0.02% of the optimized formulation. The sonicator apparatus reduced the size of vesicles; hence, the entrapment efficacy of sonicated formulations is greater than that of unsonicated formulations. The in vitro release of optimized niosomal patches formulations (TPF1-TPF2-TPF3) was performed for 6 hours across the egg membrane, where results showed that the maximum release of TPF1 formulation due to less thickness (121 ±1.53 µm) was 90.86%.

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INTRODUCTION

Skin is the major and multi-function organ of the human body, with a huge surface area (Ahmed et al., 2024). It is an available route for delivering local and systemic drugs, which minimizes the side effects of medicines delivered through other routes, such as oral and parenteral (Hashmat et al., 2020).

The benefits of drug delivery through the skin are avoiding First-pass metabolism, better patient compliance, and preventing drug irritation caused by drugs to the Gastrointestinal (GI) system (Chellappan et al., 2020). Creating a novel drug delivery method has received much attention in recent decades. Physical and chemical processes for lowering the stratum

corneum barrier characteristics have been investigated to enhance permeability (Chen et al., 2017).

Vesicles can be very useful in the delivery and targeting of active substances and modeling biological membranes (Date et al., 2005). There are various types of pharmaceutical carriers, such as cellular, polymeric, macromolecular, and particulate carriers. Lipid particles, microspheres, nanoparticles, polymeric micelles, and vesicular systems are examples of particulate-type carriers, commonly referred to as the colloidal carrier system (Farmoudeh et al., 2020).

Numerous studies have also been conducted using niosomes as a drug delivery vehicle for precise and controlled drug delivery systems. Among these, using liposomes and niosomes to improve medication penetration through the skin is common in the dermatological and cosmetic industries (Parveen et al., 2023).

However, one of the main limitations of transdermal delivery is a lower degree of permeation of hydrophilic active pharmaceutical ingredients through the skin due to the skin barrier, composed of corneocytes and fixed by lipid matrix (Malang et al., 2024). Improving the biological membrane and changing the subcutaneous layer modifies reversible lipid characteristics (Moore et al., 2021). The vesicular structure gives versatile properties to niosomes, such as non-toxic, biodegradable, and amphiphilic nature, enhancing the drug's bioavailability. Furthermore, it can modify the structure appearances, such as shape, size, nature of lamellae, and composition (Bhosale et al., 2024).

Delivery of nonsteroidal anti-inflammatory drugs over the oral route is more effective because the delivery of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) orally causes gastric irritation and ulceration; hence, transdermal delivery of NSAIDs through the skin is a technique that can prevent the above side effects and maintain the plasma level after administration of single-dose for a prolonged period (Patel et al., 2024).

Niosomes are grown from liposomes; niosomes are non-ionic single-chain surface-active agent vesicles that combine cholesterol and other components such as stabilizers (Sahu and Mohapatra, 2021). Niosomes are like liposomes with amphiphilic double-layer structures. They can be prepared as unilamellar or multi-lamellar vesicles (Saharawat and Verma, 2024). They have better Chemical stability; they are more oxidation-resistant and cost-effective, and the permeation characteristics of niosomes are much better than liposomes (Thombre et al., 2022). Niosomes have a higher capacity to incorporate more significant amounts of drugs, are biocompatible, biodegradable, non-toxic, non-immunogenic, controllable properties like size, shape, lamellarity, easy storage and handling, control release of drugs, and can be applied through different routes of administration. However, niosomes' physical stability is lower than liposomes; therefore, aggregation, hydrolysis, leakage, limited drug loading, and lower shelf life might occur during suspension, which are the major drawbacks of the formulation (Kovacik et al., 2020).

In 1997, L Oreal reported non-ionic surfactant vesicles in cosmetics formulation. Lancome, part of the Oreal group, was marketed 1980 as an anti-aging and whitening product. Recently, researchers formulated Resveratrol as a niosome for dermatological application (Faheem et al., 2024). A modified Franz diffusion cell is used to examine the permeability of niosomal formulations. This cell's donor and receptor compartments are divided by a membrane (Raihan et al., 2024).

Lornoxicam is a nonsteroidal anti-inflammatory drug used in the management of rheumatoid arthritis, soft tissue pain, post-operative pain, and migraine prophylaxis. Lornoxicam can be formulated as niosomal transdermal patches to sustain and immediately release characteristics and avoid the limitation of the oral route (high first-pass effect, short half-life, low bioavailability). Therefore, transdermal formulation can enhance the solubility and bioavailability of lornoxicam.

The following are the main objectives of this study:

- Enhance the aqueous solubility of lornoxicam;
- Increase the permeation ability of poorly water-soluble drug lornoxicam;
- Controlled and sustained the release of lornoxicam from their vesicles;
- Reduce the dose of lornoxicam when compared with the oral dosage form;
- Compared with the transdermal dosage form, it reduces lornoxicam's side effects on the gastric system.

METHODS AND MATERIALS

The thin film hydration method, known as the modified hand-shaking method, was first presented by Bangham. This multi-step process can be initiated by mixing a known amount of lipids and edge-activating agents such as Span-20, Sodium deoxycholate, Tween 20, and Brij-30 as per selection criteria. The lipid and edge activator solution is prepared in a rotary bottom flask by adding methanol and chloroform. Assemble the RBF to a rotary evaporator and rotate at a constant temperature, i.e., 60 °C, 80 rpm, and pressure is reduced to generate a vacuum. A thin film will form after evaporation of organic solvents. The thin film can be hydrated with water or a buffer solution. After hydration, it should be kept overnight to swell the lipids and form vesicles. By this method, multi-lamellar vesicles can be formed, and vesicles of the required size can be obtained by further sonication.

Sonication is the most commonly used method for the manufacture of niosomes. Two types of sonication are available: Bath sonication and Probe sonication. In probe sonication, a solution of the drug (Lornoxicam) in phosphate buffer solution is added into cholesterol and non-ionic surface-active agent mixtures; then, the whole system is permitted to sonicate for 15 min at 60°C. Sonication of this suspension and extrusion across a polycarbonate membrane filter of 100 nm gives the vesicle a suitable size—the material used is shown in Table 1.

Table 1*: Material used*

S. NO	Materials	Sources
1	Lornoxicam	Bafna pharmaceuticals
2	Span-20	S.D. Fine Chem Ltd, Boisar
3	Tween 20	S.D. Fine Chem Ltd, Boisar
4	Brij- 30	S.D. Fine Chem Ltd, Boisar
5	Sodium deoxycholate	S.D. Fine Chem Ltd, Boisar
6	Polyethylene Glycol	S.D. Fine Chem Ltd, Boisar
7	Polyethylene Glycol	S.D. Fine Chem Ltd, Boisar
8	Hydroxy Propyl methylcellulose	S.D. Fine Chem Ltd, Boisar
9	Cholesterol	Bafna pharmaceuticals
10	Distilled water	Pharmaceutics Laboratory

Experiment

Primary Screening of Surfactants in Niosome Formulations. Different surfactants, such as span 20, tween 20, brij-30, and sodium deoxycholate, were used to prepare niosomes of Lornoxicam, shown in Table 2.

Table 2*: Primary screening for selection of appropriate surfactant*

Formulation Code	Ratio of Surfactant and Cholesterol (mg)	Surfactant Used
F1	200:500	Span-20
F2	200:500	Tween 20
F3	200:500	Brij- 30
F4	200:500	Sodium deoxycholate

For the preparation of niosomes of lornoxicam, different surfactants such as span 20, tween 20, brij-30, and sodium deoxycholate are used. Among these surfactants, Brij-30 showed higher entrapment efficiency because brij-30 increases the rigidity of cholesterol; hence, the entrapment efficiency increased, as shown in Table 3.

Table 3: *Selection of surfactant in niosome formulation by entrapment efficiency*

Formulation Code	Surfactant: Cholesterol (mg)	Surfactant Used	%Entrapment Efficiency of Unsolicited Vesicles	% Entrapment Efficiency of Sonicated Vesicles
F1	200:500	Span-20	55.17 ±0.02	59.54 ±0.03
F2	200:500	Tween 20	61.34 ±0.09	66.58 ±0.04
F3	**200:500**	**Brij- 30**	**70.13 ±0.10**	**72.39 ±0.02**
F4	200:500	Sodium deoxycholate	45.34 ±0.08	53.88 ±0.05

Preparation of Niosome Formulation Containing Brij-30. The niosome vesicles were prepared using the rotary film evaporation technique. This method formed a thin layer of cholesterol in a round bottom flask, which was kept at a glass transition temperature of 60. The hydration medium phosphate buffer solution with pH 7.4 was used as a stable buffer. By keeping it overnight, proper hydration and swelling of the lipid occur; the agitation of the thin layer forms different types of multi-lamellar vesicles. After vesicles formed, all the

formulations were sonicated in a bath sonicator for 15 minutes at regular intervals to reduce vesicle size (Yang et al., 2021).

The optimized formulation was selected to prepare the transdermal niosomal patch using the formulations in Table 4. The Hydroxy Propyl Methyl Cellulose and Propylene Glycol were dissolved in water and incorporated in a niosome formulation. After mixing both of the solutions, they were stirred for a while. Finally, the solution was poured into a glass petri plate and kept overnight at room temperature. The patch is packed in aluminum foil, as shown in Figure 1.

Table 4: *Composition of niosomal patch*

S. No.	Composition	Quantity
1	Niosomal suspension	8 ml (2.5 mg Lornoxicam)
2	Polyethylene Glycol	0.5 ml
3	Hydroxy Propyl methylcellulose	1.0 g
4	Distilled water	q.s

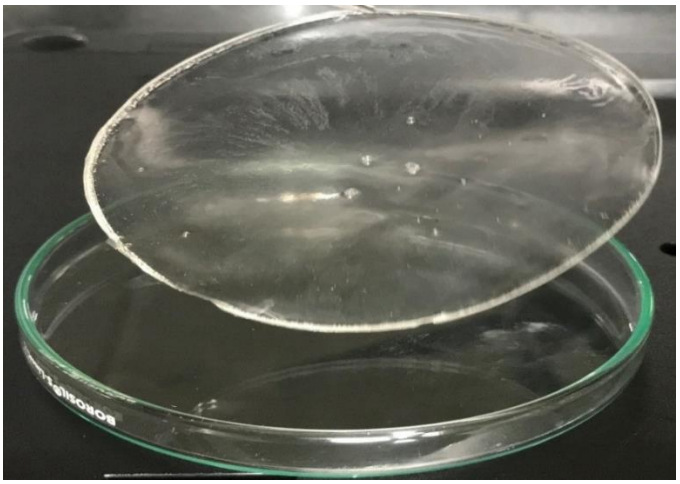

Figure 1*. Niosomal Patch of Lornoxicam*

Characterization of Niosomal Patch

Determination of the Melting Point of Lornoxicam. The melting point of Lornoxicam was 225-230°C as per specifications given in International Pharmacopeias. 2010. The melting point was measured using the capillary method. The drug was loaded into a capillary tube up to one-third of the capillary length fused from one end. The capillary tube was then kept in the electrical melting point apparatus. The temperature of the melting point apparatus was gradually increased. The melting point was carefully observed when the substance started to melt (Kassem et al., 2023).

Determination of Zeta Potential. Any particle in suspension, macromolecule, or material surface can display zeta potential, a physical characteristic. It can be applied to predict interactions with surfaces, optimize the production of films and coatings, and optimize the

formulations of protein solutions, emulsions, and suspensions. The zeta potential of F1, F2, and F3 formulations was found to be -26.5 mV, -23.0 mV, and -24.1 mV (figure 2). Every tissue, including the stratum corneum and carriers, has a negative charge on its surface. In light of this, it is hypothesized that a topical formulation with a positive charge could boost penetration due to a more significant interaction with the membrane's negative charge.

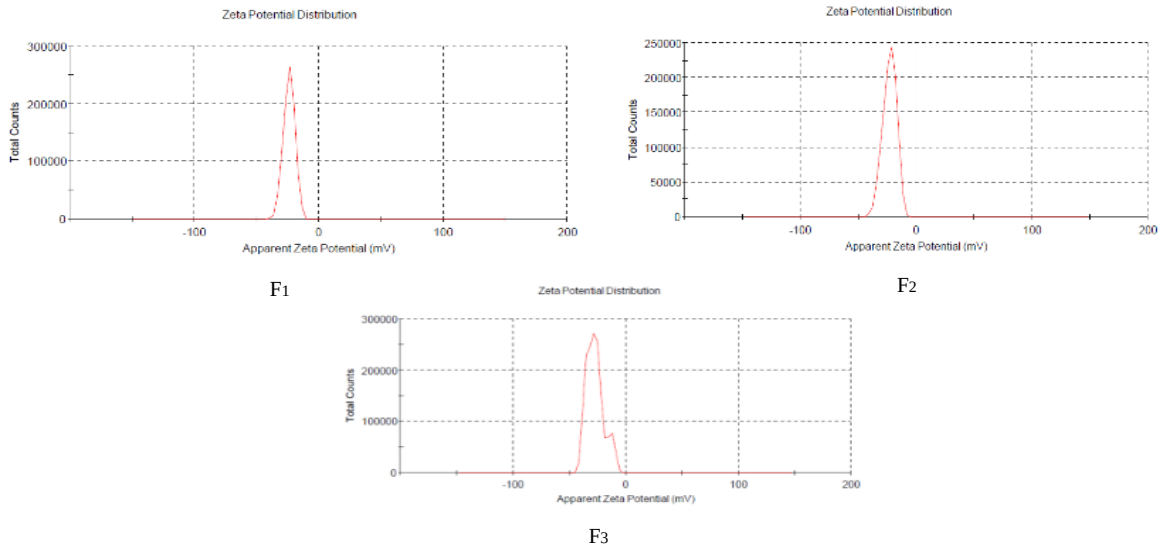

Figure 2. *Zeta Potential of Optimized Formulations*

Transmission Electron Microscopy (TEM). Using transmission electron microscopy, or TEM, a high-energy electron beam was passed through a material to image its inside structure. This configuration is comparable to the simple transmission-illuminated optical microscope (Hoseini et al., 2023). The results from drug-loaded optimized vesicular formulations (F1, F2, F3) show vesicle morphology. Niosomal vesicles were discrete and uniform. The diameter was within the range of 100-500 nm (Figure 3).

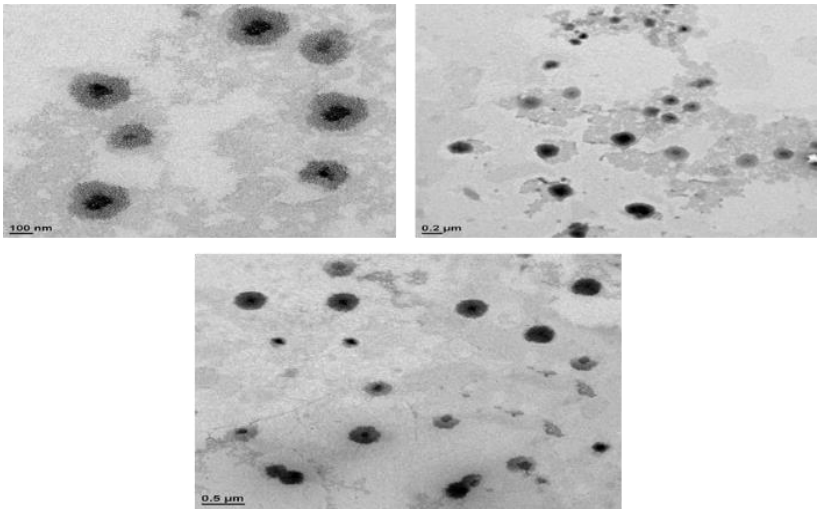

Figure 3*. TEM Images of Optimized Formulations*

Differential Scanning Calorimetry (DSC). Differential scanning calorimeter thermogram of niosomes of Lornoxicam and loaded proteasomes. Lornoxicam showed an endotherm at

213.55°C, while niosomes at 58.79°C, consistent with their melting point. Differential scanning calorimeter thermogram of Lornoxicam revealed a sharp endothermic peak at 210.57°C. Conversely, the thermogram of Lornoxicam-loaded niosomes revealed an absence of drug endothermic peak, and niosomes bilayer endotherm was shifted and showed a broad wide peak at 59.11. These results signify the possible contact of the drug with bilayer components and confirm the entrapment of Lornoxicam into the vesicles (figure 4).

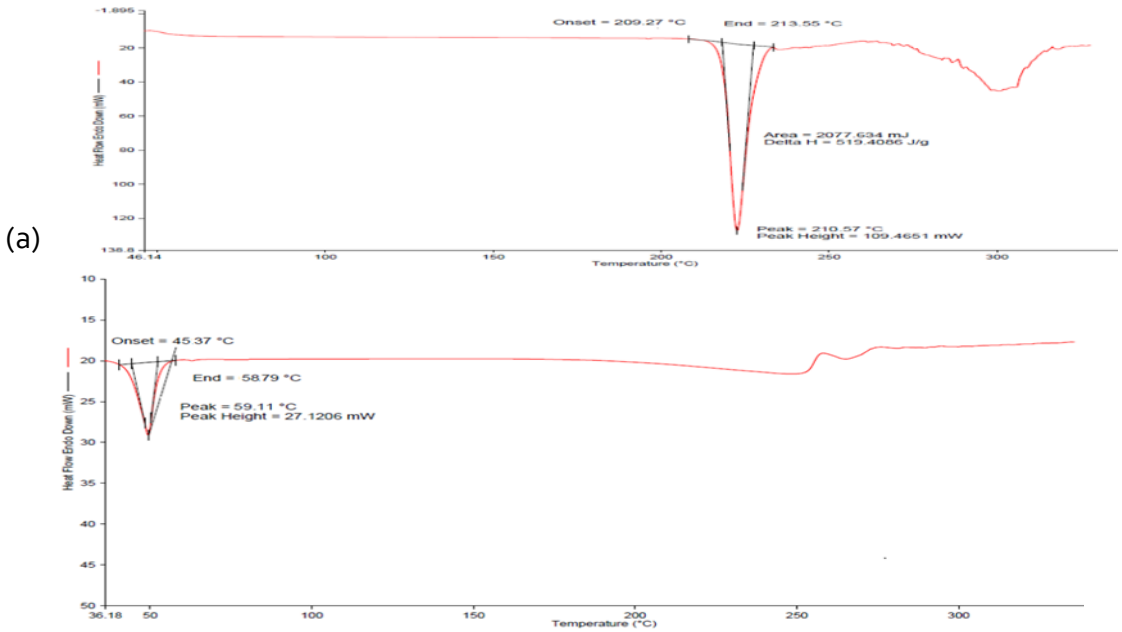

Figure 4. *DSC Spectra of (a) Pure Drug of Lornoxicam, (b) Niosomes Formulation*

Field Emission Scanning Electron Microscopy (FESEM). The FESEM images for unsolicited optimized formulations (F1, F2, F3) have shown the niosome vesicles with spherical shape and size range of 30 to 100 µm analyzed after magnification of 20000 to 80000 (figure 5).

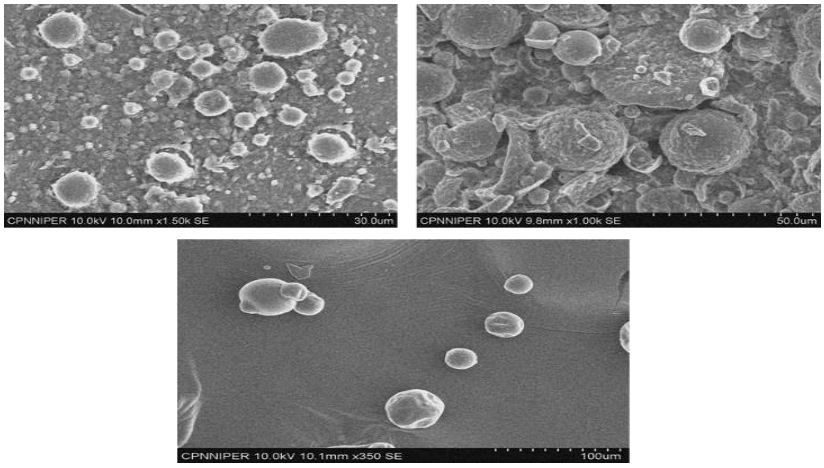

Figure 5. *FESEM Images of Optimized Formulations*

Statistical Analysis

The formulations prepared according to the design were analyzed using Design Expert® version 11 software packages. One-way ANOVA statistically evaluated the effect of

formulation variables on the response variables at 0.05 levels. The design was evaluated using the response surface method using the following equation.

P-values. Less than 0.0500 indicates that model terms are significant. In this case, A is a significant model term. Values greater than 0.1000 indicate that the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. Three duplicates of the experiments were conducted, and the mean±SD was used to report the results (Ayoubi et al., 2024).

RESULTS AND DISCUSSION

The result showed that the percentage entrapment efficacy of unsolicited niosome vesicles was 70.13% ±0.2 and sonicated 72.39% ±0.02 of optimized formulation (F3). With a sonicator apparatus, the size of vesicles is reduced. Hence, sonicated formulations' entrapment efficacy is more than unsolicited formulations. Moreover, formulations with optimized surfactant (Brij-30) showed higher entrapment efficiency because it increases the rigidity of cholesterol. The in vitro release studies of the TPF1- TPF2-TPF3 drug formulations showed a release of 90.86%, 82.13%, and 71.49% through the egg membrane, respectively. Initially, the drug release from the transdermal niosomal patch showed a sustained release and could release 80% of Lnoroxicam in almost 7 hours, as seen in the graph below (figure 6). This is a desirable result for us to prolong the release of Lnoroxicam, which would eventually prolong and sustain its anti-inflammatory effects. Also, the TPF1 formulation showed the maximum release due to less thickness (121 ±1.53 µm) was 90.86%. That can be attributed to the thickness of the transdermal patch.

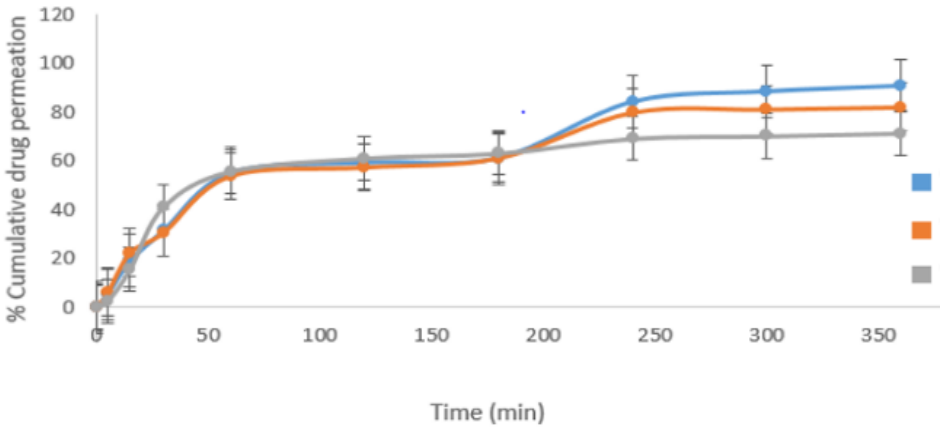

Figure 6: *In Vitro Drug Release of Different Niosomal Patch Formulations*

Some parameters have been determined, shown in Table 5; one is the thickness of transdermal patches, which has an inverse relationship with the release of medicinal substances.

Table 5. *The evaluated parameters of the Niosomal Patch of Lornoxicam*

Parameters	TPF1	TPF2	TPF3
Thickness (µm)	121 ±1.53	134 ±2.00	167 ±1.00
Moisture Content (%)	2.34 ±0.13	2.27 ±0.12	2.29 ±0.10
Drug Content (%)	94.76 ±1.64	97.33 ±1.48	96.54 ±3.70
Folding Endurance	197 ±5.03	227 ±6.11	216 ±8.33
pH	5.31 ±0.05	5.41 ±0.07	5.25 ±0.03

CONCLUSION

The results of this study reveal the effect of type and ratio of surfactant and cholesterol on the entrapment efficiency and drug release from the niosomal patch. The optimized formulation of the niosomal patch showed more than 90% entrapment efficacy. TEM electron micrographs showed spherical-shaped vesicles. Therefore, these transdermal niosomal patches can be employed as an alternative to oral Lornoxicam administration by attaining an effective therapeutic dose with increased patient compliance, reduced gastrointestinal side effects, and dosing frequency. Based on all of these investigations, patches loaded with Lornoxicam into niosomes exhibited a longer duration of action than formulations with Lornoxicam in non-niosomal form, and this formulation can be effectively developed to enhance the anti-inflammation activity.

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