Ind. J. Pharm. Edu. Res., 2026; Krupapharmacon:27-41.
https://www.ijper.org

Original Article

Development and Evaluation of Meloxicam Nanostructured Lipid Carriers for Transdermal Delivery

Nimisha Jain[1,*], Preeti Sudheer[2], M Madhan[1], Anjitha C J[1]

[1]Department of Pharmaceutics, Krupanidhi College of Pharmacy, Bangalore, Karnataka, INDIA.
[2]Nitte (Deemed to be University) Nitte College of Pharmaceutical Sciences (NCOPS), Bangalore, Karnataka, INDIA.

ABSTRACT

Background: Meloxicam is a BCS Class II NSAID, with gastrointestinal side effects and shows poor skin permeability when administered orally. Nanostructured Lipid Carriers (NLC), consisting of both solid and liquid lipids, can enhance drug stability, drug loading capacity, skin permeation, and enable controlled release, making them suitable for transdermal delivery. **Objectives:** This study aimed to develop and evaluate Meloxicam-loaded nanostructured lipid carriers for enhanced transdermal delivery and improved anti-inflammatory efficacy. **Materials and Methods:** Meloxicam was incorporated in NLCs through the hot homogenisation method using glyceryl monostearate, beeswax, carnauba wax, oleic acid and poloxamer188. A Box-Behnken design was used for optimization. The optimized formulation was characterised for drug content, particle size, zeta potential, entrapment efficiency, SEM, DSC and *in vitro* drug release. The optimized NLCs were incorporated into HPMC E15-based transdermal patches and evaluated for folding endurance, drug content, thickness, moisture content, *ex vivo* permeation studies, FTIR compatibility, anti-inflammatory activity and stability. **Results:** The optimized NLC formulation exhibited a particle size of 260.5nm and a zeta potential of -33Mv, suggesting good stability. Sustained drug release of about 92% over 24 hr was observed. *Ex vivo* permeation studies showed higher drug flux and permeability compared to pure drug patches. The NLC patch demonstrated enhanced anti-inflammatory activity and showed no significant changes during stability studies**.** **Conclusion:** Meloxicam-loaded NLC-based transdermal patches offer improved permeation, sustained release, and enhanced therapeutic efficacy, representing a promising alternative to conventional oral delivery.

Keywords: Anti-inflammatory activity, Meloxicam, Nanostructured lipid carrier, Skin permeation, Transdermal drug delivery.

Correspondence:
Dr. Nimisha Jain
Department of Pharmaceutics,
Krupanidhi College of Pharmacy,
Bangalore-560035, Karnataka, INDIA.
Email: nimijain@gmail.com

INTRODUCTION

Osteoporosis is a disorder characterized by bone fragility. Low calcium intake can raise the risk of fractures, decreased bone density and early bone loss. Men and women who are underweight and restrict their food intake lose bone density. Typically, bisphosphonates like Alendronate, Risedronate, and Ibandronate are used initially for treating osteoporosis. Recent research shows that discontinuation of medication leads to a high risk of spinal fractures. It is crucial to take the medication consistently.[1]

Postmenopausal Osteoporosis (PMO) is a prevalent skeletal condition that increases fracture risk due to reduced bone density or impaired bone quality. Early in the perimenopausal era, there is an increase in bone turnover, which results in net bone loss. Estrogen plays an important role in maintaining bone strength. However, around the menopause, typically occurring at an average age of 50, estrogen levels drop. These result in increased bone loss more quickly.[2]

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) can be used to treat osteoporosis because they reduce inflammation and pain and have a small protective effect in bones, which can improve Bone Mineral Density (BMD). NSAIDs that can be taken by mouth or injected are celecoxib, mefenamic acid, ibuprofen, indomethacin, and naproxen. Administration of NSAIDs by oral routes can cause severe side effects such as bleeding, perforation of upper GI tract and ulceration.[3]

Meloxicam is an oxicam derivative that belongs to the enolic acid class of drugs (NSAIDs). This drug is a type II Biopharmaceutical Classification System (BCS) drug. In n-octanol/buffer pH 7.4, the drug has an apparent partition coefficient (log p) app = 0.1, and its pKa values are 1.1 and 4.2. Meloxicam oral administration is in the form of a tablet and contains 7.5 mg or 15 mg of the drug. After taking a single 30 mg dose of oral capsules, the absolute

DOI: 10.5530/ijper.krupapharmacon.21

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bioavailability is 89%. But it is mostly distributed in the areas with a lot of blood flow, like the liver, kidneys, and blood.[4]

Administering medication orally can lead to adverse effects like abdominal discomfort, gastric irritation and indigestion. Prolonged usage of such medication can even result in bleeding and the formation of ulcers.

In order to mitigate the potential irritation of the drug within the gastrointestinal tract, reduce the risk of overall toxicity, and enhance the therapeutic outcomes, opting for transdermal drug administration is a viable solution.

The transdermal approach to drug administration offers several advantages, including its non-invasive nature, which circumvents the need for invasive procedures. This method also side steps the gastrointestinal side effects, making it a preferred choice for addressing both pain and inflammatory conditions. Furthermore, it contributes to a lower occurrence of systemic adverse effects compared to other routes of administration.

Various carrier approaches utilized in transdermal drug delivery include solid lipid nanoparticles, polymeric nanoparticles, microemulsion, liposomes, niosomes, Nanostructured Lipid Carriers (NLC), etc. These approaches offer advantages such as improved targeting of drugs to the skin, better tolerance at the application site, effective incorporation of lipophilic drugs, increased control over drug release rates, and efficient integration of lipophilic medications.[5]

Nanostructured Lipid Carriers (NLCs) are lipid nanoparticles with a size range of 1 to 1000 nm. They are made up of biocompatible lipids (both solid and liquid) and emulsifiers. NLC is considered a good approach because the nanosized NLC adheres to the skin and increases its permeability to the drug. They are less toxic, more bioavailable, biocompatible, have controlled release, have high drug-loading capacity, and are very stable. Lipids and surfactants, which are parts of NLC, can also help drug to pass through the skin by making the stratum corneum less of a barrier.[5]

Considering all of these points, we aimed to develop a transdermal delivery system for meloxicam based on a Nanostructured Lipid Carrier (NLC), which may increase the therapeutic potential of the drug.

MATERIALS AND METHODS

Materials

The Meloxicam sample was gifted by Strides Arcolab Bangalore, lipid and other chemicals were bought from Sigma Aldrich Mumbai.

Methods

Methods of preparation of Nanostructured Lipid Carriers (NLC)

Preliminary trials by hot homogenization technique

The blank NLC formulation was prepared by the hot homogenization technique. There were both solid and liquid lipids in the lipid phase. Beeswax, carnauba wax, and glyceryl monostearate made up the solid lipids. Oleic acid was the liquid lipid, and surfactant poloxamer 188 was the aqueous phase. The oleic acid was heated first, and then the carnauba wax, beeswax, and glyceryl monostearate were heated in a china dish above their melting point. In a beaker, the aqueous phase (aqueous surfactant) was heated. With a mechanical stirrer running at 1000rpm, the lipid phase was added to the hot aqueous phase, which made a coarse oil/water emulsion. A polytron homogenizer was used to turn the coarse emulsion into a fine emulsion. NLCs were obtained by cooling the resulting emulsion to room temperature. The physical nature of the NLC for its free-flowing nature was assessed. Based on the physical characteristics of the blank formulation drug-loaded NLCs were prepared by the addition of the drug to the melted lipid and stirring it into a melted lipid mixture (beeswax, carnauba wax, and glyceryl monostearate). Then the heated aqueous surfactant solution was added, and the previously described technique was followed.[6]

Utilization of experimental design

Quality by Design (QBD) has enhanced formulation integrity robustness by minimising the number of required tests that need to be done. Optimization of formulation and process parameters was carried out using a Box-behnken design using the drug expert trial version.[7,8]

Evaluation of responses

The experimental response data were incorporated into the design model and analysed for model fit, based on the desirability function approach. The optimum formulation is selected.

Evaluation of optimum formulation

Particle size analysis

The maximum size of nanoparticles should be 1000nm. The dynamic light scattering principle was utilized for the particle size analysis from <1 nm to >µm. The Horiba SZ-100 nanoparticle dynamic light scattering system was used to find out the zeta potential, distribution and particle size. The samples were diluted using double-distilled water and evaluated three times at a scattering angle of 90°C and a temperature of 25.2°C.[9]

Zeta potential

Nanoparticles require the zeta potential to accurately estimate their surface charge. It is essential for the physical stability of NLCs. The zeta potential of SZ-100 was measured by HORIBA Scientific. After diluting the samples with double-distilled

water, particles were measured three times at a 90°C angle using electrophoretic light scattering at 25°C.[10]

Drug content

Weigh out the NLC that is equal to 20 mg of meloxicam and transfer to a 10 mL volumetric flask, and mix with 10 mL DMSO (stock 1). From the (stock 1) 1 mL was diluted to 10 mL DMSO (stock 2), and the stock 2 preparation was diluted into 10 mL using DMSO (stock 3). The absorbance at 375 nm was measured using UV spectrophotometry.[11]

Scanning Electronmicroscopy

To study the surface morphology of the optimized formulation, Tescan Vega3 scanning electron microscopy was used. Gold was used to scatter NLC dispersion onto a sample container. The data were collected at a voltage of 10 kV while argon was being purged.[12]

In vitro release studies

The Franz diffusion cell assembly was employed to perform the *in vitro* drug release studies. The cellophane membrane was mounted between the receptor and donor compartments of the diffusion cell assembly to hold approximately 5 mg of drug equivalent weight NLC. 1 mL of pH 5.5 phosphate buffer was added to the donor compartment to moisten it. Using a magnetic stirrer at 35°C, stir the 50 mL of pH 7.4 phosphate buffer in a receptor compartment at a speed of 100-250 rpm. Every hour, 1 mL of receptor fluid was taken out to check how quickly the drug was released from NLC. The sink condition was maintained by replacing the withdrawn sample with an equal volume of Phosphate Buffer Saline (PBS). The spectrophotometric approach measured drug concentration after adequate dilution at λ_{max} of 375 nm.[12]

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) investigation confirmed the thermal behavior of pure drugs with lipid formulation. About 5 mg of sample and drug equivalent formulations were weighed and placed in non-hermetically sealed aluminium pans. The samples were heated from 0°C to 350°C at a rate of 10°C per minute. Throughout the measurement, nitrogen gas was constantly being purged at a rate of 40 mL/min, and the DSC thermograms were obtained using a Shimadzu DSC-60 instrument.[13]

Preparation of NLC-loaded patch

The solvent casting procedure described above is employed to create an NLC-loaded patch formulation. For a uniform polymeric dispersion, HPMC E15(700 mg) was carefully weighed and mixed in 10 mL of water using a magnetic stirrer. Then 2 mL of polyethylene glycol (plasticizer) was added, and thoroughly aged. Finally, Meloxicam-NLCs were introduced into the aforementioned polymeric dispersion and mixed well to ensure uniform dispersion. The resulting dispersion was then added to a clean, 57.02 cm^2 surface area petri dish. After that, the formulation-containing dish was put into the solvent hood chamber for the night with the funnel inverted to regulate the solvent's rate of evaporation. The dried MX-NLC was obtained once the solvent had completely evaporated. Using aluminium foil, the final patch is wrapped and kept in a sealed desiccator at room temperature (25°C) until additional examination is performed.[14]

Evaluation of Drug loaded patch

Drug content

An NLC patch with an area of 5 cm^2 containing 20 mg of meloxicam (theoretical drug content) was cut and transferred into a 10 mL volumetric flask containing 10 mL of DMSO (stock 1). The 1 mL of (stock 1) was diluted to 10 mL using DMSO to obtain (stock 2), and again 1 mL of (stock 2) preparation was diluted into 10 mL using DMSO to obtain (stock 3). The absorbance at 375 nm was measured by UV spectrophotometry.[14]

Thickness, folding endurance of patches and weight uniformity

A screw gauge is used to measure thickness at five separate locations. Folding endurance, a patch strip was cut uniformly and repeatedly folded at the same position until it ruptured. The average weight was computed by measuring the weight homogeneity from five randomly cut (1 cm by 1 cm) patches.

Moisture content

Following a 24-hr period at room temperature and individual weight measurements, each created patch was placed in a desiccator with activated silica until a consistent weight was reached.

Moisture uptake

The weighed patches were stored in a desiccator filled with potassium chloride solution at room temperature and 84% Relative Humidity (RH) for 24 hr. After 24 hr, the patches were reweighed, and the moisture uptake percentage was calculated and described using the formula given below.[14]

$$\%Moisture\ uptake = \frac{(final\ weight - initial\ weight)}{initial\ weight} \times 100$$

Ex vivo permeation studies

Ex vivo permeation studies were conducted after obtaining approval from the Institutional Animal Ethics Committee for the use of Wistar rats (Ethical No: KCP/IAEC/PCOL/PCEU/144/APR2024). The studies were performed using a modified Franz diffusion cell. 5 mg of meloxicam in an NLC patch, 5 mg of pure drug was placed on the abdominal region skin samples of Wistar rats separately, which was inserted between the receptor and donor compartments of the separate diffusion cells. 1 mL

of the phosphate buffer pH 5.5 is used for moisten the donor compartment. The receptor compartment consists of 50 mL of phosphate buffer with a pH of 7.4. The magnetic stirrer was used to constantly agitate the receptor compartment at 100 rpm while keeping the temperature at 35°C. By removing 1 mL of receptor fluid per hour the drug release rate from NLC was determined. The phosphate buffer was added continuously to maintain sink condition. After dilution against blank Phosphate buffer, using spectrophotometer at 375 nm the drug concentration was measured. The Drug flux (µg/hr/cm^2) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed skin surface and the permeability coefficient was determined using the following equation.

$$Jss = \frac{Q}{A \times t}$$

Jss = Steady state flux (µg/hr/cm^2); A = Area of exposed membrane (cm^2).

Q = Amount of drug transported into the membrane at time (t).

$$Permeation\ coefficient\ (kp) = Jss \times C0 - Ci$$

C0-Ci = Concentration of the drug on the donor and receptor side of the membrane (cm/hr).[15-17]

Fourier Transform Infrared Spectrum (FTIR) studies

The Meloxicam pure drug, the NLC formulation and the optimal NLC-loaded Meloxicam patch formulation were carried out for FTIR studies. An IR spectrophotometer (Thermo-Nicolet 6700) was used to measure the samples using the potassium bromide pellet method in the spectral range of 4000-400 cm^{-1}.

Study of anti-inflammatory effect

Anti-inflammatory activity was studied via carrageenan induced rat paw edema method. The animals were kept in the animal house for one week before the experiment and they were given on unrestricted supplies of water and food. Rats are considered into 2 groups; each groups comprised of 6 rats. To induce edema 0.1 mL of 1% w/v carrageenan in saline was injected into the bottom of rats right paw for 1 hr before each experiment. Group 1 was the positive control group and got 0.1 mL of 1% w/v carrageenan in saline. Group 2 received 0.1 mL of 1% w/v carrageenan in saline, and the calculated dose of nanostructured lipid carriers formulation was prepared and applied on the plantar surface of the rat hind paw. The volume of rat paw will be measured right after the carrageenan injection and then again 1, 2, 3, and 4 hr using a plethysmometer to compare against the control group.

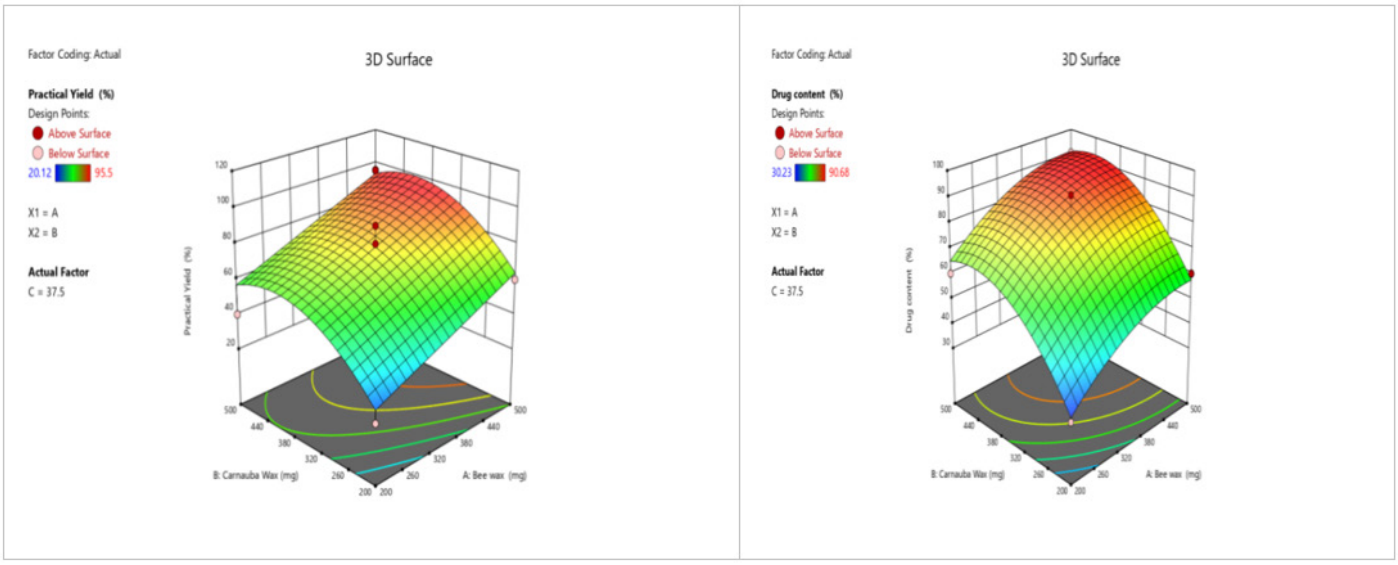


Figure 1: Surface plots of practical yield and drug content.

Table 1: Preliminary trials by hot homogenization technique.

Trials	Ratio Solid lipids: Liquid lipids	Surfactants	Observations
T1	700;300	0.020	Emulsification
T2	800:200	0.030	Emulsification
T3	900:100	0.040	Particulate matter
T4	600:400	0.050	Particulate matter
T5	500:500	0.010	Phase separation

Table 2: Experimental runs.

Formulations	Beeswax	Carnauba wax	Surfactant
NLC1	350	350	37.5
NLC2	500	200	37.5
NLC3	350	350	37.5
NLC4	200	350	25
NLC5	500	350	50
NLC6	500	200	25
NLC7	500	350	25
NLC8	350	500	25
NLC9	200	200	50
NLC10	350	200	25
NLC11	200	350	50
NLC12	350	500	50
NLC13	200	500	37.5
NLC14	200	500	25
NLC15	500	500	37.5
NLC16	200	200	37.5
NLC17	350	200	50

Table 3: Data for drug loading and percentage yield.

Formulations	Practical Yield	%Drug Content
F1	86.38±0.28	81.25±1.17
F2	88.56±0.06	69.84±3.47
F3	87.02±0.72	85.13±0.33
F4	85.35±0.32	74.5±0.42
F5	88.21±0.06	87.55±0.02
F6	89.89±0.01	88.05±0.02
F7	88.75±0.07	89.02±0.02
F8	88.45±0.06	70.11±0.02
F9	89.76±0.01	87.84±0.02
F10	90.00±0.01	85.19±0.01
F11	89.03±0.09	83.47±0.08
F12	86.99±0.01	89.05±0.03
F13	90.38±0.06	88.52±0.06
F14	92.01±0.07	95.09±0.02
F15	86.38±0.06	81.25±0.01
F16	88.56±0.01	69.84±0.01
F17	87.02±0.03	85.13±0.05

Stability studies

The NLC-incorporated patch formula was tested for three months at 25°±2°C/60% RH± 5% and 40°C ± 2°C/75% RH ± 5% in stability investigations of NLCs. At the halfway point of the trial period, the formulations, drug content and physical nature were examined.

RESULTS AND DISCUSSION

Preparation of NLC by Preliminary trials

The preliminary studies were carried out on the basis of the ratio of solid and lipid concentration ranges were considered. Appropriate ratios of liquid and solid lipids, along with a specified quantity of surfactants, were used in the preliminary trials. Based on the aforementioned trials, different ranges of carnauba wax, beeswax, and surfactants were considered for the trial runs. Table 1 represents Preliminary trials.

Utilization of experiment of custom design

The formulations were optimized by Quality by Design (QBD) screening with parameters on the quality criteria via Box Behnken design using Design expert trial version. Beeswax, Carnauba Wax and Surfactants were selected as formulation factors while drug content and practical yield were chosen as response variables. Experimental trials were conducted, and the formulations were assessed for the drug content and practical yield. The experimental design produced 17 experimental runs, as represented in Table 2.

Drug Content

To prepare NLCs, the heat homogenization process was applied. JMP 13 was used in a custom design method to optimize the formulations. The selection of parameters included the ratio of solid lipids to liquid lipids and quantity of surfactant. The replies that were selected were drug content and percentage yield Table 3 represents the data of drug loading and % yield.

Percentage yield

The drug content was 95.09±0.012%SD, with a percentage yield of 92.01±0.017%SD. Despite having a high surfactant content in this composition. When solid lipid and oil are combined, phase separation produces lipid nanodroplets surrounded by a solid matrix. The lipid matrix present on the oil surface prevents drug leakage from the inner core, delaying the release of the drug Table 3 represents data of drug loading and %yield.

Evaluation of Experimental design and summary of response evaluation

To achieve the desired properties in formulation, procedure optimization regarding constituent quantity and process parameter settings is crucial. A Custom design is an experimental design that can effectively address various issues within a framework. Therefore, a statistical analysis was conducted, the custom design technique was chosen, and the essential formulation variables were evaluated.

ANOVA for the reduced quadratic model Response of practical yield.

Table 4 represents the Response of the practical yield.

Table 5 represents the Fit response of practical yield.

Final Equation of Actual factors

Practical yield = -96.79086 +0.121883(beeswax)+0.658174(carnauba wax)-0.000799(carnauba wax)

Response 2: Drug content.

ANOVA for Reduced Quadratic Model.

Table 6 represents the Response of drug content.

Table 7 represents Fit response of the drug content.

Final Equation of Actual Factors

Drug content = -98.73023+ 0.298460(beeswax)+ 0.538173(carnauba wax) -0.000304(beeswax2)- 0.000611(carnauba wax2)

Coefficients of Coded Factors.

Table 8 represents coefficients of Coded factors.

Table 4: Response of the practical yield.

Source	Sum of Squares	d_f	Mean square	F value	*p* value
Model	5799.46	3	1933.15	28.44	<0.0001
A Bee wax	2674.00	1	2674.00	39.33	< 0.0001
B-Carnauba Wax	1756.17	1	1756.17	25.83	0.0002
B^2	1369.29	1	1369.29	20.14	0.0006
Residual	883.76	13	67.98		
Lack of Fit	723.27	9	80.36	2.00	0.2625
Pure Error	160.49	4	40.12		
Cor Total	6683.22	16			

Table 5: Fit response of practical yield.

Std dev	Mean	c.v.%	R^2	Adjusted R^2	Predicted R^2	Adeq Precision
8.25	69.87	11.80	0.8678	0.8372	0.7374	17.3429

Table 6: Response of drug content.

Source	Sum of Squares	d_f	Mean square	F value	*p* value	
Model	4550.59	4	1137.65	52.56	<0.0001	significant
A-Bee wax	1310.77	1	1310.77	60.56	< 0.0001	
B-Carnauba Wax	2196.25	1	2196.25	101.48	< 0.0001	
A^2	198.14	1	198.14	9.15	0.0106	
B^2	798.02	1	798.02	36.87	< 0.0001	
Residual	259.72	12	21.64			
Lack of Fit	123.00	8	15.37	0.4498	0.8438	Not significant
Pure Error	136.72	4	34.18			
Cor Total	4810.31	16				

Table 7: Fit response of drug content.

Std dev	Mean	c.v.%	R^2	Adjusted R^2	Predicted R^2	Adeq precision
4.65	72.25	6.44	0.9460	0.9280	0.8995	23.2810

Table 8: The coefficient in terms of coded factors.

Factor	Coefficient Estimate	d_f	Standard Error	95% CI low	95% CI High	VIF
Intercept	81.94	1	1.85	77.92	85.97	
A-Bee wax	12.80	1	1.64	9.22	16.38	1.0000
B-Carnauba Wax	16.57	1	1.64	12.99	20.15	1.0000
A^2	-6.85	1	2.26	-11.78	-1.92	1.00
B^2	-13.75	1	2.26	-18.68	-8.81	1.00

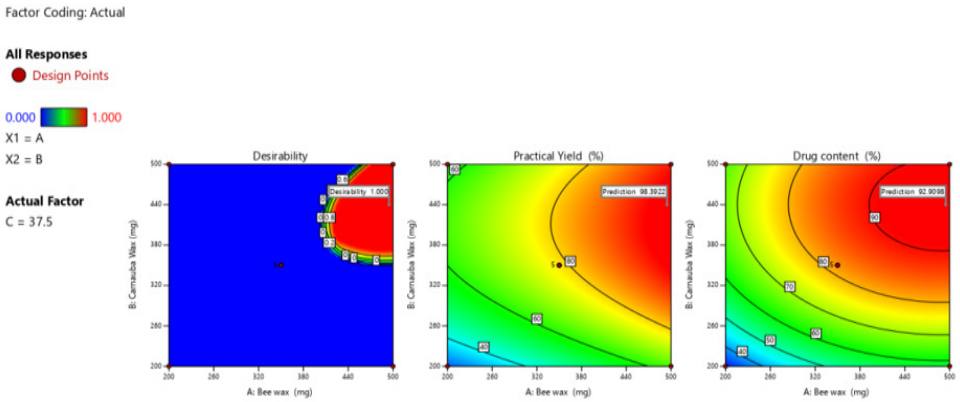


Figure 2: Contour plot.

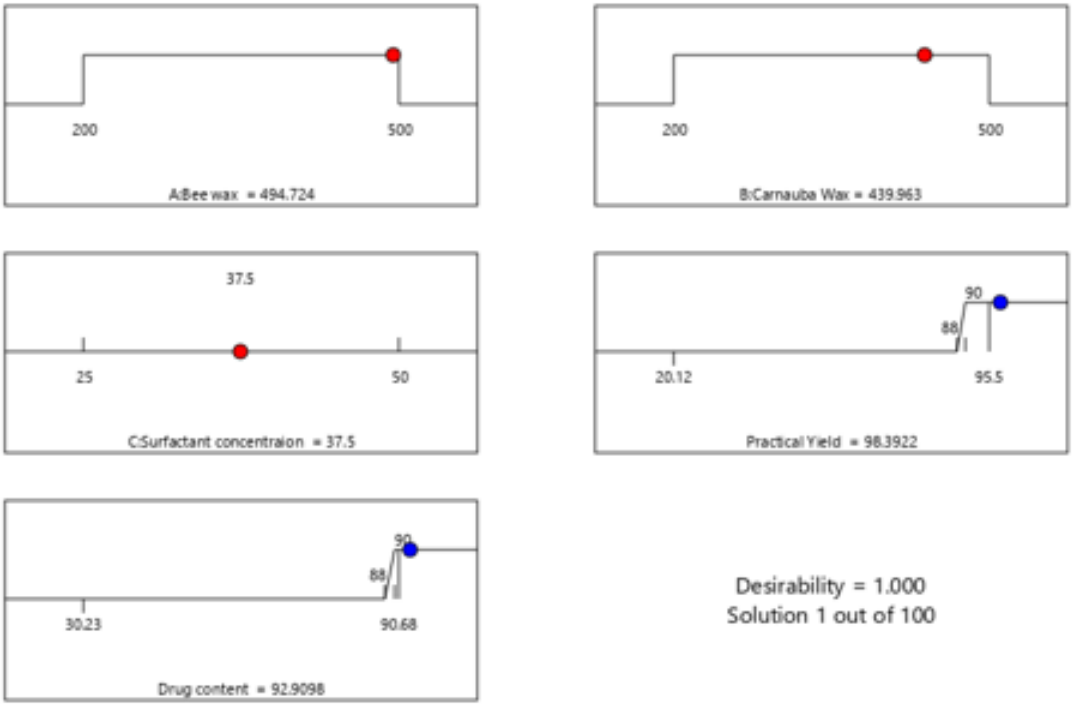


Figure 3: Maximum desirability graph of practical yield and drug content.

Surface response curves

Surface response curves offer an effective method of analysis in determining possible compromise. Surface response graphing methods like contour plots and surface plots help determine desirable responses. The contour plot represents the response surface in two-dimensional form, while the surface plot illustrates the response surface in three dimensions.

The surface plots exhibited only first-order effects without any higher-order interactions, indicating absence of curvature effects.

3D surface plot of drug content and practical is shown in Figure 1.

Contour plots are given in Figure 2.

Numerical optimization

Numerical optimization gives the maximum desirability graph of drug content and practical yield is given in Figure 3.

Evaluation of optimized formulation

Particle size distribution

The ideal formulation's average particle size, according to the particle size study, was determined as 260.5 nm.

Zeta Potential

The electrokinetic potential, also known as zeta potential, provides information on the magnitude of the inter-electrostatic repulsion between neighbouring particles present in a dispersion. The more stable the distributed system, the higher the zeta potential value. The calculated zeta potential was -33 mV, indicating that NLCs are stable and that there is no higher-level agglomeration in the system.

Scanning electron microscopy

Particles with somewhat agglomerated surfaces and uneven surfaces are visible in the surface picture. One possible reason for the unevenness could be that the high stirring speed causes the lipids' structure to become disoriented. This kind of surface morphology may have been caused by the drug-containing liquid phase occasionally ejecting during the solidification process, creating an enlarged liquid phase shell on the solid surface Figure 4 represents SEM images of the optimized formulation.

Drug Release Profile

Comaparative in vitro drug release profile

The formulation exhibited drug release of 92.41±0.24% over a 24 hr study period. In drug release, the spatial arrangement of solid-liquid domains is crucial. The structure of the nanoparticles

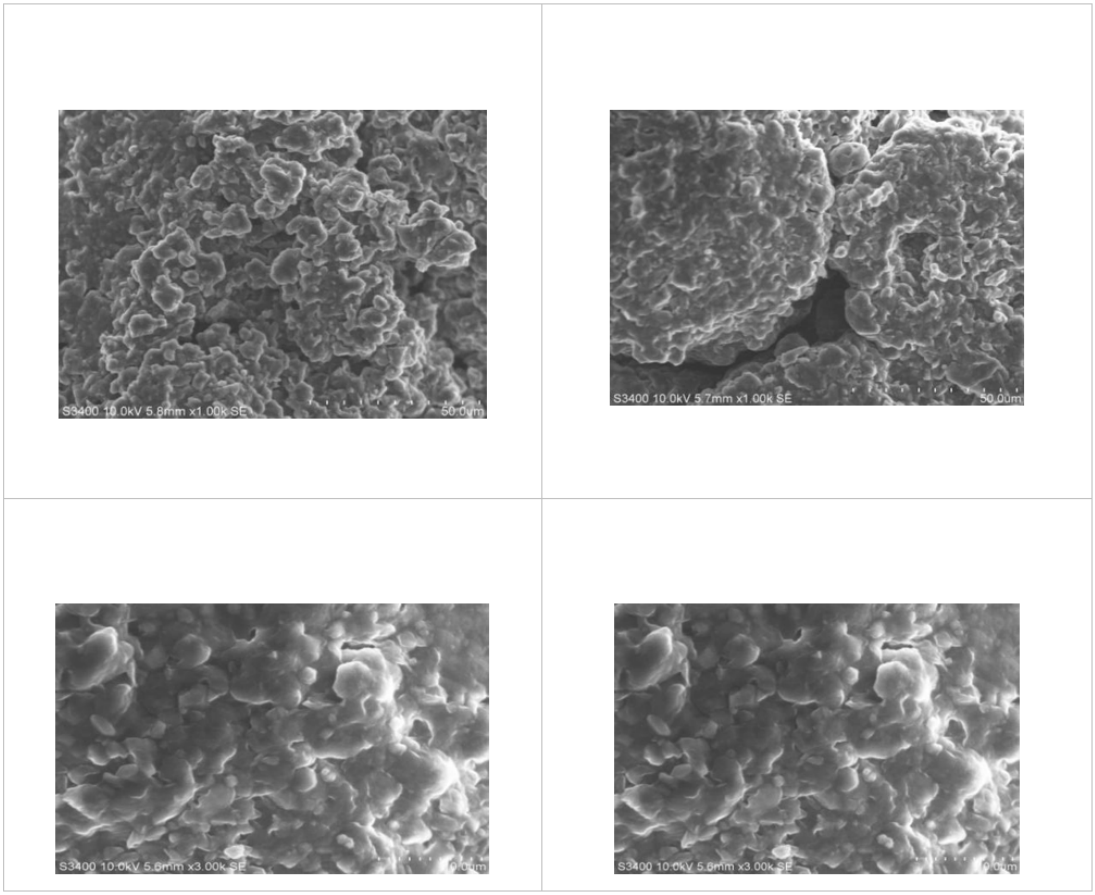


Figure 4: SEM images of optimized formulation.

influences how quickly the medicine is released. Drug release occurs in normal lipid systems when the drug molecules are uniformly distributed inside the lipid matrix and then diffuse across the lipid systems. The presence of fluid-natured lipid in NLCs can raise the medications' diffusion coefficients, favoring a faster drug release Table 9 represents Comparative invitro drug release profile Figure 5 Represents Comparative *in vitro* Release.

Differential Scanning Calorimeter (DSC)

Using DSC, the thermal properties of meloxicam and Meloxicam-loaded NLC were examined to determine how the lipids affected the drug. The thermogram of meloxicam results shows an endothermic peak at 270.3°C. The endothermic peak in the modified formulation moved to a lower temperature of 239.12°C, respectively. This suggests that the surfactant and lipids (oleic acid, beeswax, and carnauba wax) may have lowered the NLC of meloxicam's melting point. This would have favorably affected its retention inside the lipid matrix, and when it comes into contact with aqueous media, it demonstrates a reversal effect, thus enhancing the release of medication Figure 6 represents DSC Results.

Table 9: Comparative *in vitro* release profile.

Time	Pure Drug ±SD	MX-NLC±SD
0	0	0
1	5.56±0.02	10.22±0.08
2	10.56±0.23	25.33±0.32
3	21.36±0.35	37.76±0.29
4	27.54±0.09	48.32±0.16
5	35.62±0.12	58.36±0.41
6	42.55±0.13	68.24±0.12
7	47.66±0.02	80.23±0.26
8	53.11±0.05	82.23±0.18
24	59.71±0.26	92.41±0.24

Preparation of optimized meloxicam-loaded NLC patch

The optimized formulation obtained from the prediction model revealed 95±0.01% entrapment efficiency, 91.09±0.012% of the drug content and 260.5 nm particle size. The patches were prepared with polyethylene glycol as a plasticizer and hydroxypropyl methyl cellulose polymer. The ability of NLC to dissolve into the stratum corneum's lipid layers, or lipid dynamic behavior, is responsible for its higher skin penetration as compared to pure drug patches and commercial formulations. The skin distribution of meloxicam is therefore facilitated by lipid exchange between the carrier lipid and the stratum corneum. Second, these carriers can penetrate the deeper layer of skin because of their size. While most of the particles are likely to associate with the stratum corneum, thereby altering the barrier properties of the skin, increasing medication penetration, only a small number would likely remain intact on the skin's surface. Thirdly, poloxamer played a part in the drug's ability to penetrate skin. Because surfactants can change the aqueous fluid content and disturb the ordered stratum corneal layers, they may have increased skin penetration.

Evaluation of patch

The pharmaceutical composition of the patch formulation drug content was determined to be 94.9±0.06%, the thickness 0.110±0.08 mm, the folding endurance 236.2±3, the weight

Table 10: Drug content, thickness, folding endurance, weight uniformity, and moisture content.

Drug Content (%)±SD	Thickness±SD (mm)	Folding Endruance ±SD	Wt Uniformity (mg) ±SD	Moisture Content (%)±SD
94.9±0.06	0.110±0.08	236.2±0.05	192±1.3	1.5±0.09

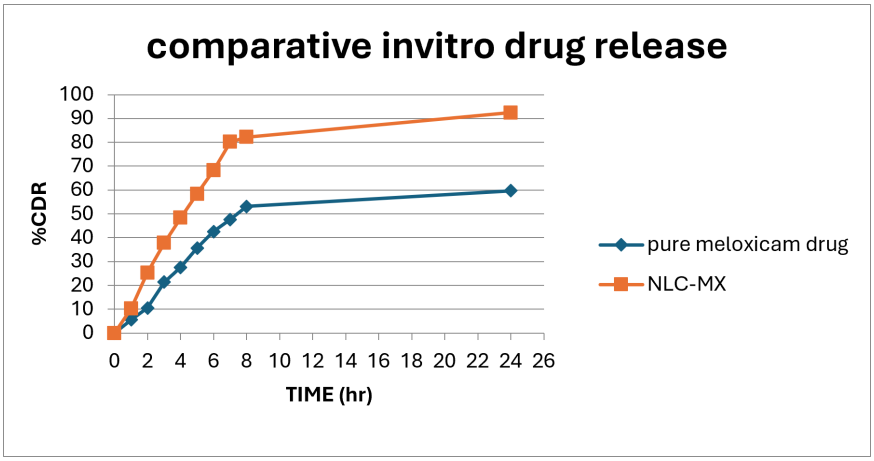


Figure 5: Graphical Representation of Comparative *in vitro* Drug Release.

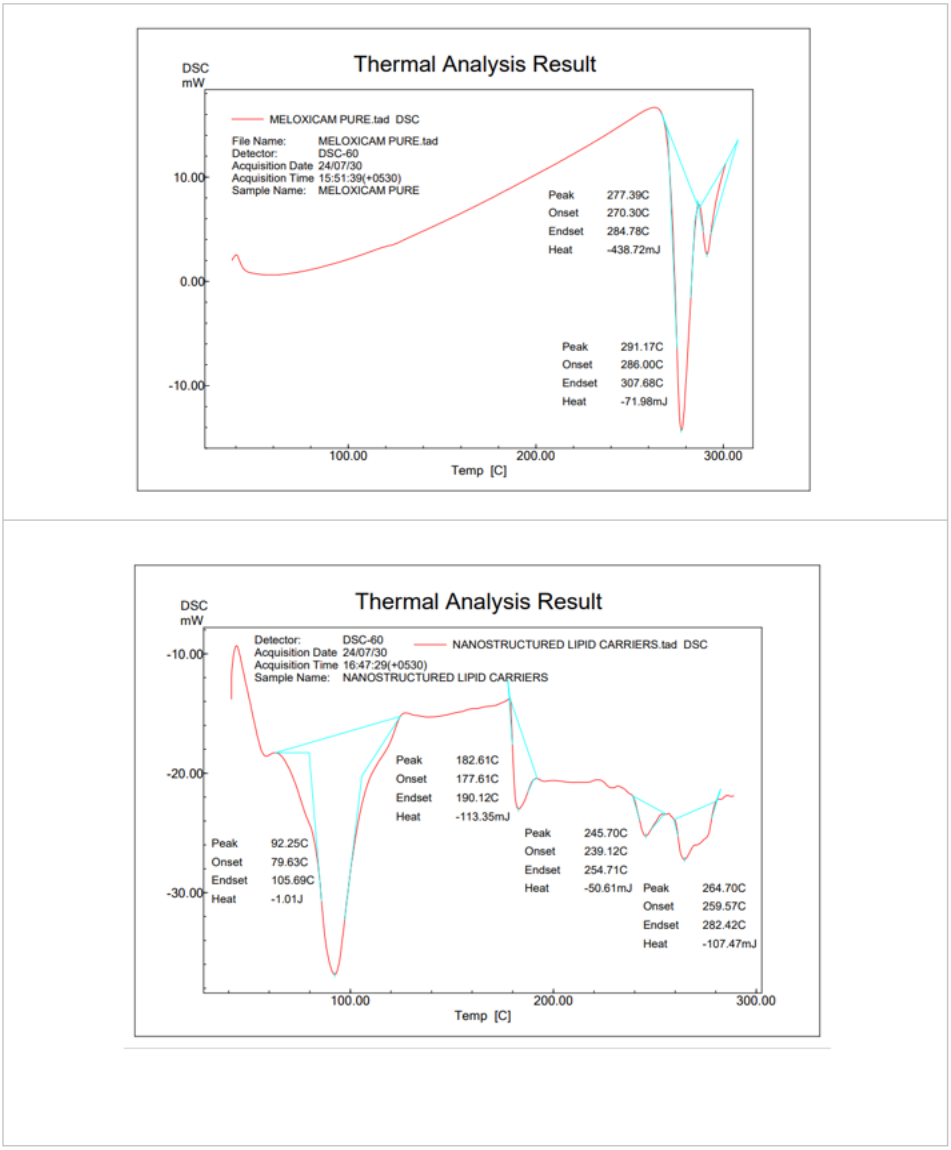


Figure 6: DSC thermograms.



Figure 7: *Ex vivo* study in Franz diffusion cell.

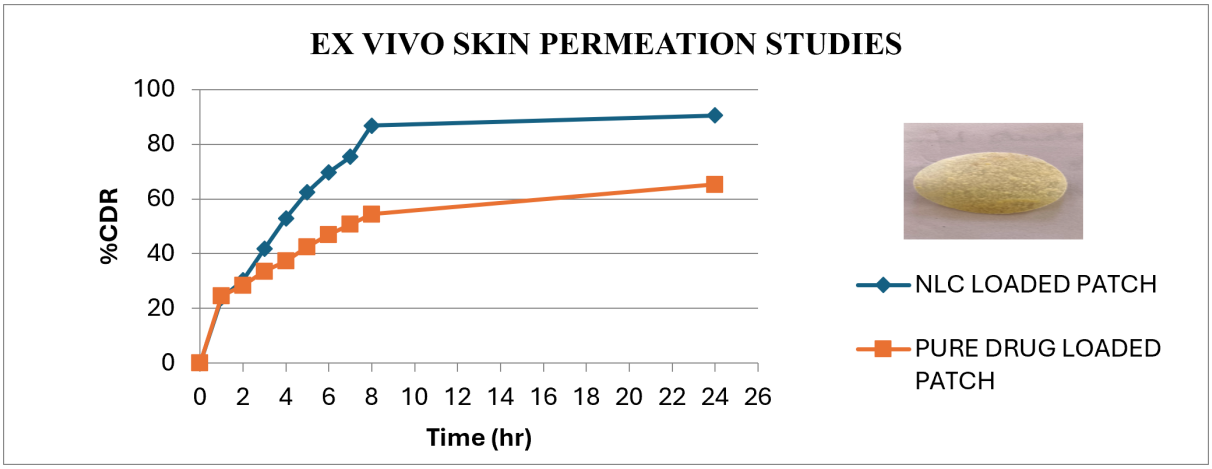


Figure 8: *Ex vivo* skin permeation studies: Graphical representation.

Table 11: ***Ex vivo*** **skin permeation tabular column.**

Time	NLC Loaded Pastch±SD	Pure Drug Loaded Patch±SD
0	0	0
1	23.88±0.003	24.62±0.012
2	30.23±0.002	28.35±0.003
3	41.79±0.019	33.58±0.017
4	52.98±0.006	37.31±0.001
5	62.54±0.014	42.53±0.002
6	69.74±0.006	47.01±0.001
7	75.36±0.001	50.74±0.013
8	86.85±0.016	54.47±0.007
24	92.14±0.008	65.24±0.005

variation 192±1.3 mg, and the moisture content 1.5±0.09% Table 10 represents the evaluation of the patch.

Ex vivo permeation studies of optimized formulation compared with meloxicam-loaded patch and marketed patch

According to 24-hr release studies presented in Table 11, the drug penetration rate from NLC patch was found to be 92.14 ±0.08%, compared with the pure drug. The commercialized meloxicam patch (2.5%) demonstrated a permeation rate of 90.15±0.007%, respectively. The NLC formulation demonstrated action for up to 24 hr, peaking at 6 hr, confirming the patch's extended activity. The commercial formulation, on the other hand, had higher action during the first eight. This may be linked to the presence of a sizable amount of alcohol, which is known to improve skin penetration. At 24 hr, however, the commercial formulation showed less activity. The pure medication, however, showed action for up to 8 hr. It was established that the created NLC patch's quicker start of effect was equivalent to that of the commercial gel. Encapsulation, or the process of phase separation that occurs when oil and solid lipid are combined to form nanodroplets of oil encased in a solid matrix, may account for the NLC patch's continuous activity even after 24 hr. Drug release is slowed down because the lipid matrix surrounding the oil phase stops the drug from leaking out of the inside Table 11. Represents *ex vivo* skin permeation tabular column Figure 7 represents *ex vivo* studies in franz diffusion cell.

Comparative *ex vivo* drug release studies

Ex vivo permeation studies of optimized Meloxicam-NLC patch in comparison with a pure drug-loaded patch and the marketed patch formulation. The optimized formulation Meloxicam-NLC patch exhibited a drug permeation rate of 92.14%, whereas the pure drug-loaded patch, showed a permeation rate of 65.24% in 24 hr. The developed NLC formulation demonstrated sustained drug release for up to 24 hr, confirming the prolonged drug release characteristics of the patch formulation Table 12 represents the comparative steady state flux and permeability coefficient Figure 8 represents a graphical representation of *ex vivo* skin permeation studies.

FTIR spectroscopy studies

FTIR studies were carried out for the meloxicam drug, the NLC meloxicam physical mixture, and the NLC meloxicam patch formulation is shown in Figure 9. All observed ranges were within the stretching ranges. Meloxicam, both in NLC and patch preparation, had characteristic peaks.

Anti-inflammatory studies

Prostaglandin, leukotrienes, histamine, bradykinin, TNF-α, and other inflammatory and proinflammatory mediators are released when carrageenan is used. Acute inflammation goes through two phases. The first phase begins immediately after the injection of phlogistic agent and is associated with the release mediators such as serotonin, histamine, and kinins. In contrast, the second phase occurs within 2-3 hr and involves the release of prostaglandin. Both steroidal and nonsteroidal anti-inflammatory drugs are known to inhibit this second phase. Prostaglandin plays a major

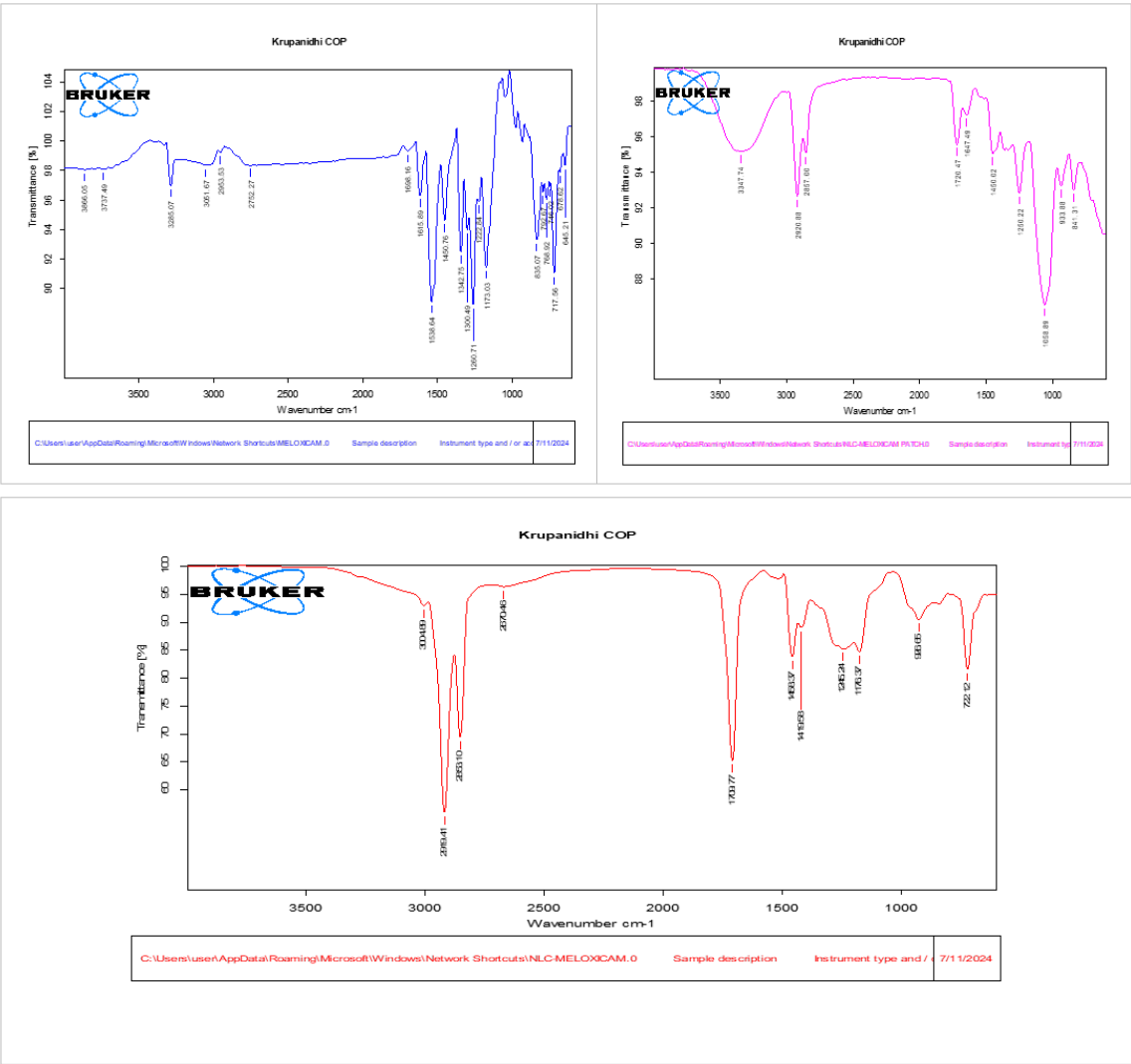


Figure 9: FTIR spectrum of (a) meloxicam pure drug, (b) NLC-meloxicam optimized. formulation, (c) NLC- meloxicam patch formulation.

Table 12: Comparative Steady State flux and permeability coefficient.

Time (hr)	Steady state flux jss	
	Pure drug-loaded patch	NLC loaded patch
1	0.12±0.01	0.25±0.03
2	0.14±0.06	0.36±0.07
3	0.16±0.08	0.47±0.09
4	0.22±0.09	0.55±0.03
5	0.26±0.04	0.64±0.08
6	0.32±0.06	0.75±0.06
7	0.34±0.02	0.86±0.06
8	0.42±0.08	0.95±0.03
Permeability coefficient Kp ($cmhr^{-1}x10^{3}$)		
Kp	Pure drug-loaded patch	NLC loaded patch
1	0.32	0.57

role in acute inflammation. An anti-inflammatory drug that blocks prostaglandin and the inflammatory pathway is present in the developed optimized formulation of the NLC incorporated patch. Following carrageenan injection into the hind paw, the edema gradually increased and peaked after 4 hr. Every hour, the paw thickness of group 1 animals increased, and this increase was statistically significant at $p<0.001$. The average increase in rat paw thickness at 24 hr was 1.57 ± 0.02. Group 2 animals mean paw thickness increased by 1.38 ± 0.05 at the end of the1st hr, and by 1.44 ±0.08 at the end of 2nd hr. Following the 2nd hr, it dropped to 1.1±0.001, 0.93±0.07, 0.77±0.02 and 0.63±0.08 after 3, 4, 5 and 24 hr. Thus, Group 2 showed a significant reduction in rat paw thickness ($p<0.001$). According to the results, the prepared optimized formulation, Meloxicam NLC-incorporated patch, inhibits the initial stage of carrageenan-induced paw edema, indicating its anti-inflammatory properties Table 13 represents the anti-inflammatory studies results. Figure 10 represents the anti-inflammatory study

Table 13: Results of anti-inflammatory studies.

Groups	Treatment	Mean Increase in Paw Volume at Different Hours ±SD						
		0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	24 hr
1	Positive control 0.1 mL of 1% w/v carrageenan in saline							
		1.23±0.09	1.42±0.02	1.61±0.01	1.82±0.003	1.73±0.008	1.69±0.05	1.57±0.02
2	Transdermal formulation treated group 2nd stage: Application of NLC after the onset of inflammation using carrageenan							
		1.22±0.009	1.38±0.05	1.44±0.08	1.1±0.01	0.93±0.07	0.77±0.02	0.63±0.08

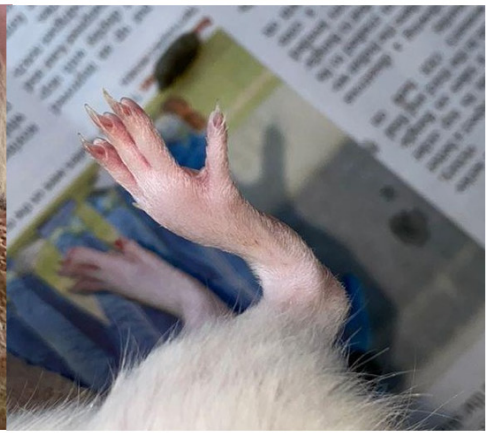


(a) Plethismograph

(b) Healthy rat paw



(c) Injection of carrageenan



(d) Carrageenan induced inflamed

Figure 10: Anti-inflammatory activity.

Table 14: Stability studies.

Temperature and Relative Humidity	Physical Nature	Drug Content
at 25°C ± 2°C/ 60% ± 5% RH and 40°C ± 2°C/75% ± 5% RH	No change	93.89±0.025

Stability studies

Accelerated Short-term stability studies were carried out for 90days at storage conditions of 25°C ± 2°C /60% ± 5% RH and 40°C ± 2°C / 75% ± 5% RH on ideal NLC formula and NLC-loaded patch. The physical appearance result indicates that the attributes remain unchanged at the above-mentioned storage conditions. It demonstrates that more stable conditions are provided by 25°C ± 2°C RH than by 40°C ± 2°C RH Table 14 represents stability studies.

CONCLUSION

Nanostructured Lipid Carriers (NLCs) are an effective collodial medication delivery system for transdermal application because of their numerous skin benefits. Because they are composed of non-irritating lipids, and non-toxic they are beneficial for damaged or inflamed skin. Meloxicam-loaded NLC was created for transdermal delivery in this study to minimize severe systemic side effects, lengthen its duration of action and boost medication. Meloxicam was successfully transformed into NLCs by using natural lipids, including oleic acids, carnauba wax, glyceryl monostearate and beeswax. Poloxamer was a good emulsifying agent in this oil-and-water mixture. Hot homogenization was an effective approach for producing NLCs with improved product attributes. The approach produced NLCs with sufficient drug content that flowed freely. The Box-behnken design experimental design proved suitable for obtaining the best formulas. All the formulations produced really nanosized particles, with the exception of greater zeta potentials, which indicate stability; the zeta potential demonstrates the NLCs' good stability. IR tests ensure that medications and excipients are compatible even after they have been formulated. The comparative drug release profile ensured that NLCs permeated the skin more effectively than drug-loaded patches and the commercialized patch. The nanoparticulate colloidal drug delivery system for meloxicam based on carnauba wax, oleic acid, beeswax and poloxamer is anticipated to offer clinicians a novel option for an inexpensive, dependable, and competent skin administration regimen.

ACKNOWLEDGEMENT

The study was carried out with support of the Krupanidhi College of Pharmacy Administration. For these efforts, the authors are grateful.

ABBREVIATIONS

PMO: Postmenopausal Osteoporosis; **NSAIDs:** Non-Steroidal Anti-Inflammatory Drugs; **BMD:** Bone Mineral Density; **II:** Type II; **BCS:** Biopharmaceutical Classification System; **log Papp:** Apparent partition coefficient; **pKa:** Acid dissociation constant; **GI:** Gastrointestinal; **NLC:** Nanostructured Lipid Carrier; **NLCs:** Nanostructured Lipid Carriers; **QbD:** Quality by Design; **SZ-100:** Nanoparticle Dynamic Light Scattering System; **DMSO:** Dimethyl Sulfoxide; **UV:** Ultraviolet; **SEM:** Scanning Electron Microscopy; **PBS:** Phosphate Buffered Saline; **DSC:** Differential Scanning Calorimetry; **HPMC E15:** Hydroxypropyl Methylcellulose E15; **MX-NLC:** Meloxicam-Loaded Nanostructured Lipid Carrier; **RH:** Relative Humidity; **IAEC:** Institutional Animal Ethics Committee; **FTIR:** Fourier Transform Infrared Spectroscopy; **IR:** Infrared; **TNF-α:** Tumor Necrosis Factor-α; **ANOVA:** Analysis of Variance; **3D:** Three-Dimensional; **JMP:** JMP Statistical Software; **SD:** Standard Deviation; **kV:** Kilovolt; **nm:** Nanometer; **µm:** Micrometer; **µg/hr/cm²:** Micrograms per Hour per Square Centimeter; **Jss:** Steady-State Flux; **kp:** Permeability Coefficient; **Q:** Amount of Drug Transported; **A:** Area of Exposed Membrane; **t:** Time; **C0:** Initial Drug Concentration (Donor Side); **Ci:** Drug Concentration (Receptor Side); **P:** Probability Value.Top of FormBottom of Form

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ETHICAL APPROVAL

The animal study protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC), Krupanidhi College of Pharmacy, Bangalore, Karnataka, India (Approval No: KCP/IAEC/PCOL/PCEU/144/APR-2024, dated:05/04/2024). All animal experiments were carried out following the guidelines of the Committee for purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

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Cite this article: Jain N, Sudheer P, Madhan M, Anjitha CJ. Development and Evaluation of Meloxicam Nanostructured Lipid Carriers for Transdermal Delivery. Indian J of Pharmaceutical Education and Research. Krupapharmacon 2026:27-41.