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Formulation and Characterization of Meloxicam Solid Lipid Nanoparticles in a Topical Gel for Improved Anti-Inflammatory Therapy

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This research focused on the formulation and evaluation of solid lipid nanoparticles (SLNs) for improved delivery of Meloxicam as topical gel formulation, an anti-inflammatory drug. Meloxicam and various excipients, including phospholipon 80, pluronic F68, and stearic acid, were utilized to prepare SLNs through a sonication and homogenization method. The prepared SLNs were characterized for particle size, polydispersity index (PDI), zeta potential, drug loading, and entrapment efficiency. The SLN formulation demonstrating optimal parameters was incorporated into a gel for further evaluation. The in vitro drug release study revealed significant differences in the release profiles, with SLNF-2 showing the highest and most sustained release.

Kinetic modelling indicated that the drug release from SLNF-2 followed zero-order and Korsmeyer-Peppas models, suggesting a consistent and controlled release. FTIR and DSC studies confirmed the compatibility of Meloxicam with the excipients, and SEM analysis highlighted differences in surface morphology that could impact drug release. Permeation studies using pig ear skin showed that the SLN gel provided a more prolonged and controlled drug release compared to a free drug gel, suggesting its potential for enhanced therapeutic efficacy and patient compliance.

Keywords: Solid Lipid Nanoparticles, Meloxicam, Sustained Drug Release, Topical Gel Formulation, Permeation Study.

1. Introduction

Solid lipid nanoparticles (SLNs) represent a cutting-edge drug delivery system engineered to improve the bioavailability and therapeutic effectiveness of poorly water-soluble drugs. These nanoparticles are constructed from biocompatible and biodegradable lipids that remain solid at room and body temperatures, stabilized by surfactants. The lipid matrix of SLNs can encapsulate both hydrophilic and lipophilic drugs, making them a versatile platform for diverse therapeutic applications (Aanisah et al., 2023, Abbasalipourkabir et al., 2012, Abd-El-Azim et al., 2023, Abd-Rabou et al., 2018, Abo-Zalam et al., 2021). One of the primary advantages of SLNs is their ability to enhance drug bioavailability by increasing solubility and enabling controlled, sustained release, which is particularly beneficial for drugs with poor water solubility. This controlled release reduces dosing frequency, thereby improving patient compliance and minimizing side effects. Moreover, SLNs provide a protective environment for labile drugs, shielding them from degradation caused by environmental factors such as light, oxygen, and moisture. The biocompatibility and biodegradability of SLNs, derived from their physiological lipid composition, reduce the risk of toxicity and adverse reactions, making them suitable for various administration routes, including oral, topical, and intravenous. Furthermore, SLNs can be surface-modified with ligands for targeted delivery to specific cells or tissues, enhancing therapeutic effects while minimizing systemic side effects, which is particularly advantageous in treating diseases like cancer and infectious diseases (Lingayat et al., 2017, Mehnert and Mäder, 2012).

SLNs are prepared using several methods, including high-pressure homogenization, microemulsion, solvent evaporation, and double emulsion techniques, with high-pressure homogenization being the most commonly employed due to its scalability and reproducibility. This method involves dispersing a lipid melt in an aqueous surfactant solution under high pressure to form nanoparticles. SLNs have broad applications across pharmaceuticals, cosmetics, and nutraceuticals. In pharmaceuticals, they are used for delivering anticancer agents, antibiotics, and anti-inflammatory drugs (Akanda et al., 2015, Akbari et al., 2016, Akbari et al., 2024, Akel et al., 2021, Al-Amin et al., 2016). In cosmetics, SLNs are used to deliver active ingredients in skincare products, enhancing stability and penetration. In nutraceuticals, SLNs improve the bioavailability of dietary supplements. Despite their numerous benefits, SLNs face challenges such as limited drug loading capacity and potential stability issues during storage. Future research aims to address these challenges by optimizing

formulation techniques and exploring new lipid materials. Advances in nanotechnology and materials science are expected to further enhance the functionality and applicability of SLNs, positioning them as a promising tool in drug delivery and therapeutic management (Mehnert and Mäder, 2012, Yadav et al., 2013).

Incorporating solid lipid nanoparticles (SLNs) into gel formulations significantly enhances the efficacy and stability of topical and transdermal drug delivery systems. SLN gels combine the benefits of nanoparticles and gel matrices, offering improved drug solubility, bioavailability, and sustained release while ensuring ease of application and increased patient compliance. SLNs protect encapsulated drugs from degradation caused by environmental factors such as light, oxygen, and moisture. The gel matrix further stabilizes the nanoparticles and controls the drug release rate, allowing for a prolonged therapeutic effect (Naseri et al., 2015). Enhanced permeation through the skin is another advantage of SLN gels, as lipid nanoparticles can penetrate deeper into the epidermis, delivering drugs more effectively than conventional formulations. The ease of application is a significant benefit, as gels provide a non-greasy, easily spreadable formulation comfortable for patients to use, enhancing compliance, especially for chronic conditions requiring long-term treatment. Additionally, SLNs can be designed to target specific cells or tissues, and when incorporated into a gel, they can localize the drug to the intended site of action, minimizing systemic side effects and maximizing therapeutic benefits (Yadav et al., 2013, Hou et al., 2003).

The preparation of SLN gels involves formulating SLNs through processes like high-pressure homogenization or sonication and then incorporating them into a gel base made of polymers such as carbopol, xanthan gum, or hydroxyethyl cellulose. The gel base is prepared by hydrating the polymer in water and neutralizing it with agents like triethanolamine to achieve the desired consistency (Paliwal et al., 2020). The mixture is homogenized to ensure uniform distribution of SLNs within the gel matrix, and the gel is allowed to stabilize to maintain the nanoparticles' structural integrity. Characterization and evaluation of SLN gels include assessing physical appearance and homogeneity, measuring particle size and zeta potential for stability, and conducting viscosity and rheological studies to determine spreadability and thixotropy. In vitro drug release studies and permeation studies using skin models, such as pig ear skin, evaluate the drug's release profile and its ability to penetrate the skin (Mukherjee et al., 2009, Garud et al., 2012). SLN gels are used in various therapeutic areas, including anti-inflammatory treatments, pain management, and skin care, particularly benefiting conditions requiring localized and sustained drug delivery. Future research aims to optimize SLN gel formulations by exploring new polymers, enhancing drug loading capacities, and improving nanoparticle stability within the gel matrix. Advances in nanotechnology and material science are expected to further enhance the efficacy and versatility of SLN gels, positioning them as a promising tool for targeted and controlled drug delivery in dermatology and beyond (Garud et al., 2012, Müller et al., 2000).

The rationale for fabricating Meloxicam-loaded solid lipid nanoparticles (SLNs) into a topical gel formulation is grounded in the need to enhance the therapeutic efficacy and patient compliance associated with the treatment of inflammatory conditions. Meloxicam, a nonsteroidal anti-inflammatory drug (NSAID), is widely used for its potent anti-inflammatory and analgesic properties. However, oral administration of Meloxicam is often associated with gastrointestinal side effects and fluctuating plasma drug levels. To address these issues,

incorporating Meloxicam into SLNs and subsequently into a topical gel offers several advantages (Manjunath et al., 2005). Firstly, SLNs provide a protective lipid matrix that can encapsulate Meloxicam, enhancing its stability and preventing degradation due to environmental factors such as light, oxygen, and moisture. This encapsulation also facilitates a controlled and sustained release of the drug, which is crucial for maintaining consistent therapeutic levels and reducing the frequency of application. The lipid matrix in SLNs enhances the solubility and bioavailability of Meloxicam, ensuring more efficient drug delivery to the targeted site (Manjunath et al., 2005). Secondly, the topical gel formulation offers a non-invasive and patient-friendly mode of drug administration. Gels are easy to apply, non-greasy, and provide a cooling effect, which can be particularly soothing for inflamed areas. This mode of delivery bypasses the gastrointestinal tract, thereby minimizing the risk of systemic side effects commonly associated with oral NSAIDs. The gel matrix also allows for the incorporation of a high concentration of SLNs, ensuring adequate drug loading and therapeutic efficacy (Jenning and Gohla, 2001, Weber et al., 2014).

Furthermore, the incorporation of Meloxicam-loaded SLNs into a gel enhances the drug's penetration through the skin. SLNs, due to their small size and lipid composition, can penetrate deeper into the epidermis, delivering the drug more effectively to the site of inflammation. This targeted delivery not only enhances the therapeutic effect but also reduces the risk of systemic absorption and associated side effects. Lastly, the combination of SLNs and gel provides a synergistic effect that enhances the overall stability, release profile, and therapeutic efficacy of Meloxicam. The gel matrix stabilizes the SLNs, preventing aggregation and ensuring a uniform distribution of nanoparticles. This stability is crucial for maintaining the integrity and performance of the formulation during storage and application. In assumption, the fabrication of Meloxicam-loaded SLNs into a topical gel formulation addresses the limitations of conventional Meloxicam delivery methods by enhancing drug stability, providing controlled and sustained release, improving bioaavailability, and offering a patient-friendly and effective mode of application. This approach promises to improve therapeutic outcomes and patient compliance in the management of inflammatory conditions. Taking into account all of these, this present study aimed to fabricate and develop solid lipid nanoparticles of Meloxicam followed by developing topical gel formulation of the solid lipid nanoparticles.

2. Materials and Methods

Materials

We received a free sample of Meloxicam from Alkem Laboratories in Baddi, India. A gift sample of phospholipon 80 was organised by Seachem Pharma, Mumbai, India. Pluronic F68 and stearic acid were purchased from Himedia Chemicals in Mumbai, India. Every other reagent utilised in this investigation was analytical grade.

Formulation of SLNs

The drug and the cosurfactant were weighed out and combined with enough methanol to dissolve them both. After adding acetone to the lipid, it was swirled for a while. The same temperature was maintained for both of these mixes. After some time, these two solutions were combined. After that, a probe sonicator was used to sonicate it for roughly fifteen minutes.

The oil phase was defined by this solution. A measured amount of surfactant was dissolved in a calculated amount of distilled water in a different beaker and heated for a while. The aqueous phase consisted of this solution. These two phases were combined at this point. After that, it was homogenised for roughly 7-8 minutes at a speed of 15,000 rpm using a high-speed homogenizer. To stop the aggregation of smaller-sized particles, the homogenised solution was sonicated once more for roughly twenty minutes. After that, the prepared mixture was magnetically agitated for approximately thirty minutes. Next, Whatman filter paper was used to filter it. After that, the filtrate was centrifuged for 20 minutes at 20,000 rpm. The resulting sediment contains the targeted solid lipid nanoparticles. Solid lipid nanoparticles that are dried are obtained by lyophilizing the sediment (Dasgupta et al., 2013).

Table 1. Formulation table

Formulation Code	Drug (%w/v)	Stearic acid (%w/v)	Pluronic F68 (%w/v)	Phospholipon (%w/v)	Water (%v/v)
SLNF-1	0.020	1	1.5	0.020	100
SLNF-2	0.020	1	1	0.020	100
SLNF-3	0.020	1	2	0.020	100
SLNF-4	0.020	1	1.5	0.020	100
SLNF-5	0.020	1.25	1	0.020	100
SLNF-6	0.020	0.750	1	0.020	100
SLNF-7	0.020	1.25	2	0.020	100

Characterization of the prepared SLNs

Particle size, zeta potential values, drug loading, entrapment efficiency, and in vitro release tests were used to characterise the produced SLNs. The SLN formulation that demonstrated the best values for the aforementioned parameters was then put into gel form, and it was used for additional studies (surface morphology and in vivo efficacy trials using an appropriate animal model).

Particle size and Zeta potential

The Zeta Potential Analyser was used to analyse the particle size and Zeta potential of all the samples. Zeta Potential Analyser used the Dynamic Light Scattering Technique to measure the produced nanoparticles' particle size.

Drug loading and Entrapment efficiency

The SLN sediment collected from the centrifugation operation was stored in a refrigerator in order to calculate the drug content. A precise amount of acetonitrile was used to dilute one millilitre of this sediment. A UV Visible spectrophotometer was used to evaluate this sample at a wavelength of 362 nm. The drug content was used to determine the formula for calculating drug loading, which was stated as:

Drug loading (%) = Drug content / Drug content + weight of lipid x 100

The measure that establishes how much drug is entrapped in the lipid core of the formulation is called entrapment efficiency. It shows whether there is sufficient drug in the formulation—

entrapped by the lipid—to cause the intended response. It is ascertained using the provided formula:

Entrapment efficiency (%) = Drug content /Amount of drug initially added x 100

Invitro drug release studies from the prepared SLNs

To assess the drugs released from each of the manufactured solid lipid nanodispersions, a twenty-four-hour release study was conducted. The inverted test tube approach was used to conduct the release investigation. For this, Dialysis Membrane 70 (Himedia, Mumbai, India) was utilised. The release study test tube was thoroughly cleaned, dried, and rinsed. It was filled with 1 millilitre of the manufactured nanodispersion. After cutting the membrane to the proper size to fit the test tube's mouth, it was securely fastened around the test tube's neck with thread. The drug release medium, 200 ml of freshly made Phosphate Buffer 5.8, was then filled with the inverted test tube. Throughout the release study period, this was magnetically swirled and kept at 37 +/- 0.5 ℃. Following designated time intervals of 1, 2, 4, 6, 8, 10, and 12 hours, respectively, 1 millilitre of sample was extracted and an equivalent volume of buffer was introduced into the release solution. After adding a certain amount of acetonitrile solvent to the samples, they were subjected to spectrophotometric analysis at 362 nm (Khodaverdi et al., 2013).

Drug release kinetic study

To interpret the drug release kinetics from the formulations, several kinetic models were used, including the Higuchi model (cumulative percentage of drug released vs. square root of time), the Zero order (cumulative amount of drug released vs. time), the First order (log cumulative percentage of drug remaining vs. time), the Korsmeyer-peppas model, and the Hixson Crowell model. The best-fit model was selected using the highest regression values (R^2) for the formulations' correlation coefficients.

Drug excipient interaction study

Fourier Transform Infrared Spectra (FTIR) spectroscopy

All of the functional groups that are present in the sample can be identified by their distinctive peaks using the FTIR. All of the components (drug, lipid, surfactant, cosurfactant, and their physical combination as well as the formulation of the SLN) were exposed to FTIR tests in order to monitor the occurrence of any undesired interactions (if any) and to guarantee appropriate drug entrapment. The Shimadzu model 8400 IR Spectrophotometer was used to record the IR spectra, which ranged from 400 to 4000 cm-1.

Differential Scanning Calorimetry (DSC) Analysis

Heat is always exchanged when a substance undergoes structural modification. For example, heat may be absorbed during melting or released during sublimation, crystallisation, or other processes. DSC is intended to monitor these heat exchanges during programmes with regulated temperatures and to provide conclusions about the sample's structural characteristics. Heat flow as a function of temperature or time is indicated by the signal that is acquired in DSC measurements. DSC Parkin Elmer Jade (USA) instrument was used for the DSC of the SLN sample.

Optimization of the prepared SLNs

Particle size, zeta potential, drug loading, entrapment efficiency, electron microscopy, and in vitro drug release are some of the characteristics that were taken into consideration while selecting the SLN dispersion that displayed the best values. These data were then utilised in additional studies.

Incorporation of the SLN dispersion into the gel form

The following method was used to prepare the SLN gel and a typical free drug gel: In two separate beakers, 10% glycerol, 69.5% distilled water, and 0.5% carbopol 934 were added. The mixtures were magnetically agitated for approximately an hour. After then, one of the gels received 20% of the SLN dispersion while being continuously stirred. To the other gel, the same quantity of free medication (found in the 20% SLN dispersion) was added. The gels' pH was brought down to about six after each gel was neutralised with one or two drops of triethanolamine. After that, these hydrogels were kept at room temperature and additional research was done (Verma and Alpana, 2014).

Evaluation of the prepared SLN gel

The prepared solid lipid nanoparticle (SLN) gel was evaluated based on several parameters. Firstly, the physical appearance and homogeneity of the gel were visually assessed, revealing a clear, thick, and homogenous consistency. Secondly, the spreadability of the gel was measured to determine its ease of application. This was done by placing 1 gram of the gel between two horizontal plates (20 x 20 cm^2) with a standardized weight of 220 grams tied to the upper plate. The spreadability was calculated using the formula: Spreadability = M x L / t, where M is the mass tied to the upper plate, L is the length of the glass plate, and t is the time taken for the gel to spread. Thirdly, viscosity measurements were conducted to characterize the rheological and viscoelastic properties of the water-based SLN gel. Given that SLN dispersions typically contain a lipid matrix of 10-20% and 80-90% water, they tend to be less viscoelastic by nature. Lastly, a permeation study was carried out using pig ear skin to assess the gel's ability to deliver the drug through the skin. These evaluations provide a comprehensive understanding of the physical properties and performance of the SLN gel for topical delivery

Permeation study through pig ear skin:

Preparation of the pig ear skin

The pig's ear was bought from the local butcher shop. The tap water was used to clean it and remove any garbage or foreign objects. The hairs were carefully removed with scissors, then shaved off in a gentle manner to preserve the skin's surface. A pair of scissors and forceps were used to open up the dermis and remove some tissue and subcutaneous fat. In a 2 m sodium bromide solution, it was then immersed for 36 hours. Once the dermis was removed, the pig epidermis was obtained using a knife and forceps. Once cleansed with distilled water, the resultant epidermis is used in further studies.

In vitro permeation study using pig ear epidermis

In order to place the dermal side of the pig ear skin epidermis in touch with the fluid inside the receptor compartment, it was carefully placed between the donor and the receptor

compartment in the Franz Diffusion cell. On the skin's epidermal side, 1 gm of Meloxicam SLN gel was applied and placed on the cell's donor side. 50 millilitres of phosphate buffer 5.8 were added to the receptor compartment, and the Diffusion Cell's temperature was kept at 37 +/- 0.5°C. The receiver chamber was magnetically stirred while the entire assembly was maintained on a magnetic stirrer. Samples were taken out of the receptor solution and replaced with new receptor solution after predetermined time intervals for a duration of 12 hours. After diluting the extracted aliquots with the appropriate medium, the drug content was measured spectrophotometrically at a wavelength of 260 nm (Herkenne et al., 2006).

Permeation data analysis

Plotting the cumulative amount of Meloxicam permeated per unit Pig skin epidermis area (µg/cm2) against time allowed for the construction of the SLN gel's permeation profile via the epidermis. Using linear regression analysis, the steady state flux (Jss µg/cm2/hr) of Meloxicam was determined from the plot's slope. The following formula was used to get the drug's permeability coefficient (Kp) through the membrane.

$Kp = Jss/C$

Where, C is the drug's starting concentration in the donor compartment. Using the following formula, the penetration enhancing effect was determined in terms of enhancement ratio (Er).

Er = Jss of SLN dispersion/Jss of control

3. Results and Discussion

Characterization of the prepared Meloxicam solid lipid nanoparticles:

The data presented in Table 2 provides valuable insights into the characteristics of various solid lipid nanoparticle (SLN) formulations (SLNF-1 to SLNF-7) in terms of particle size, polydispersity index (PDI), zeta potential, drug loading, and entrapment efficiency. The particle sizes of the formulations vary significantly, with SLNF-1 having the largest particle size at 1250 nm, while SLNF-2 and SLNF-3 have much smaller particle sizes of 226.51 nm and 257.82 nm, respectively. Smaller particle sizes are generally preferred for better stability and enhanced permeation, making SLNF-2 potentially advantageous in these areas. Other formulations, such as SLNF-4 (355.44 nm), SLNF-5 (668.19 nm), SLNF-6 (531.56 nm), and SLNF-7 (379.00 nm), fall between these ranges. The PDI values indicate the size distribution of nanoparticles. SLNF-3 and SLNF-7 have a PDI of 1.00, indicating a broad size distribution and potentially less stable formulations. In contrast, SLNF-2 shows the lowest PDI at 0.234, suggesting a more uniform and stable particle size distribution. A lower PDI is preferred as it indicates uniform particle size distribution, with SLNF-2 displaying the most desirable PDI. Zeta potential values reflect the surface charge and stability of the nanoparticles. All formulations exhibit negative zeta potential values, indicating stability against aggregation. SLNF-2 and SLNF-7 have the highest negative zeta potential at -24.5 mV, suggesting good stability, while SLNF-4 has the lowest zeta potential at -16.6 mV, indicating relatively lower stability. Higher absolute values of zeta potential are indicative of more stable formulations, with SLNF-2 and SLNF-7 being the most stable.

Drug loading and entrapment efficiency are critical for evaluating the effectiveness of the

formulations. SLNF-2 exhibits the highest drug loading (0.692 ± 0.077%) and high entrapment efficiency (71.3 ± 2.12%). SLNF-1 has a lower drug loading (0.668 ± 0.082%) but comparable entrapment efficiency (66.9 ± 1.11%). SLNF-3, although having a small particle size, shows the lowest drug loading (0.328 ± 0.081%) and lower entrapment efficiency (65.6 ± 1.09%). SLNF-6 and SLNF-7 show moderate drug loading and lower entrapment efficiencies compared to SLNF-2. Higher drug loading and entrapment efficiency indicate more effective formulations, with SLNF-2 being the best in this regard. In conclusion, SLNF-2 stands out as the most promising formulation with its small particle size, low PDI, high negative zeta potential, and superior drug loading and entrapment efficiency. These characteristics suggest that SLNF-2 is likely to offer better stability, uniformity, and drug delivery performance compared to other formulations. SLNF-1, despite its larger particle size, also shows good drug loading and entrapment efficiency but may face challenges in stability and permeation. SLNF-3, with its low drug loading, may not be as effective despite its small size. Overall, SLNF-2 is the most balanced and efficient formulation among the ones evaluated.

Table 2. Particle size (nm), PDI, Zeta potential (mV), % Drug loading and % Entrapment efficiency

Formulation code	Particle size (nm)	PDI	Zeta potential (mV)	% Drug loading (Mean + S.D) *	% Entrapment efficiency (Mean + SD) *
SLNF-1	1250.00	0.274	-22.7	0.668+ 0.082	66.9 + 1.11
SLNF-2	226.51	0.234	-24.5	0.692 + 0.077	71.3 + 2.12
SLNF-3	257.82	1.00	-18.5	0.328 + 0.081	65.6 + 1.09
SLNF-4	355.44	0.773	-16.6	0.449 + 0.092	67.5 + 2.01
SLNF-5	668.19	0.388	-17.8	0.499 + 0.041	62.6 + 2.03
SLNF-6	531.56	0.321	-21.7	0.526 + 0.052	53.9 + 1.15
SLNF-7	379.00	1.00	-24.5	0.588 + 0.081	57.4 + 1.21

* n= 3

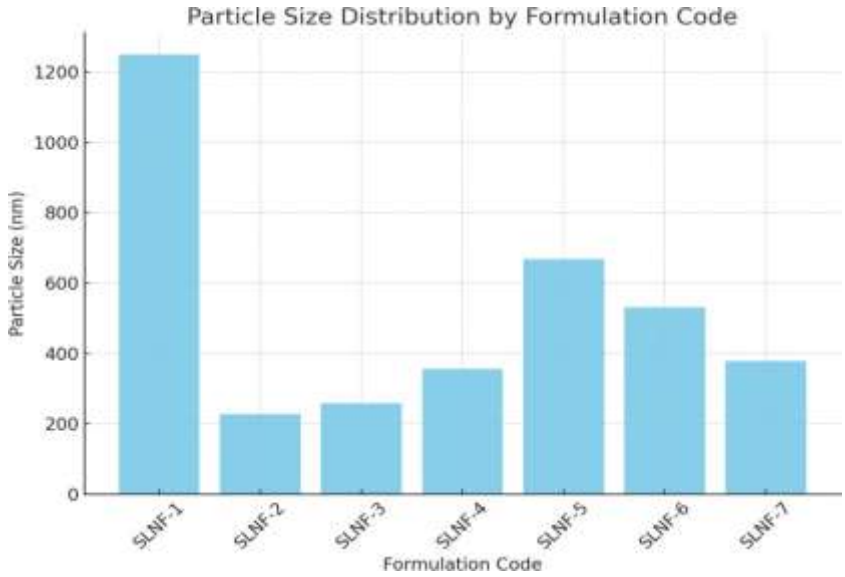

Figure 1. Particle Size Distribution

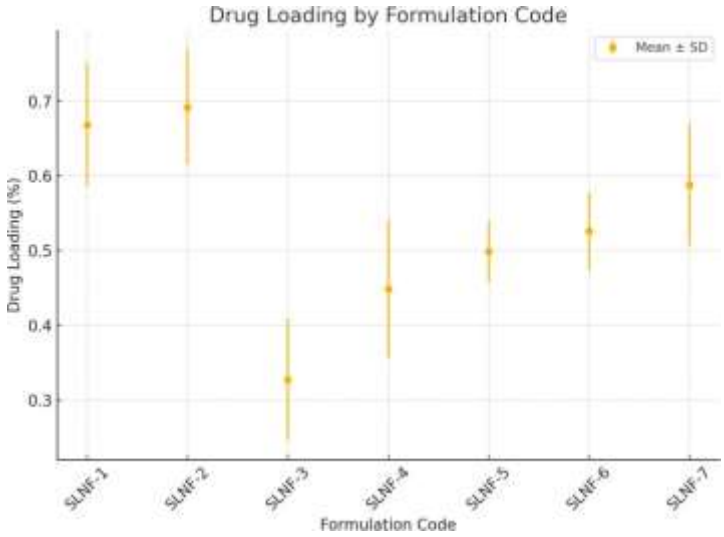

Figure 2. Drug Loading

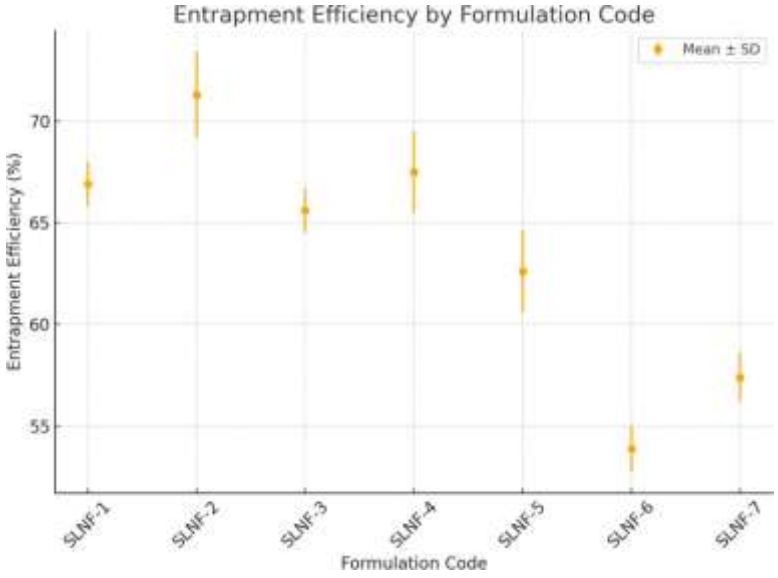

Figure 3. Entrapment Efficiency

In vitro release study

The in vitro release study of the SLN formulations (SLNF-1 to SLNF-7) over various time points reveals significant differences in drug release profiles. At the 1-hour mark, SLNF-2 exhibits the highest drug release at 69.92%, followed closely by SLNF-1 at 69.52% and SLNF-3 at 65.32%. SLNF-6 shows the lowest release at 37.12%. By the 2-hour mark, SLNF-2 continues to demonstrate superior performance with a release of 76.79%, while SLNF-1 and SLNF-3 also maintain high release rates of 71.72% and 72.22%, respectively. At 4 hours,

SLNF-2's release reaches 79.82%, with SLNF-1 and SLNF-3 following at 74.52% and 73.12%. This trend persists at 6 hours, where SLNF-2 achieves 82.04% release, SLNF-3 reaches 76.12%, and SLNF-1 shows 75.28%. At 8 hours, SLNF-2 continues to lead with 82.05% release, while SLNF-3 and SLNF-1 exhibit 78.82% and 75.38%, respectively. At the 10-hour mark, SLNF-2 maintains its highest release at 82.82%, followed by SLNF-3 at 81.12% and SLNF-1 at 75.79%. Finally, at 24 hours, SLNF-2 achieves the highest overall release at 83.02%, with SLNF-3 and SLNF-1 showing 81.52% and 77.75%, respectively. SLNF-6 and SLNF-7, while initially showing lower release rates, gradually increase over time, indicating a more controlled and sustained release profile. At 24 hours, SLNF-6 and SLNF-7 reach 50.02% and 52.52%, respectively. The high performance of SLNF-2 can be attributed to its smaller particle size and low PDI, which enhance drug release due to increased surface area and uniformity. Overall, SLNF-2 stands out as the most effective formulation for sustained drug release, followed closely by SLNF-1 and SLNF-3. These formulations are ideal for applications requiring both immediate and prolonged therapeutic effects. Conversely, SLNF-6 and SLNF-7, with their more controlled release profiles, are suitable for maintaining consistent drug levels over extended periods. The study highlights the importance of particle size and PDI in optimizing drug release from SLN formulations.

Table 3. In vitro release study

Formulation code	Time (hrs)	% Drug release from SLN dispersion						
		SLNF1	SLNF2	SLNF3	SLNF4	SLNF5	SLNF6	SLNF7
SLNF-1	1	69.52 + 1.54	69.92 + 1.35	65.32 + 1.00	62.02 + 1.04	41.52 + 1.64	37.12 + 1.22	42.32 + 1.90
SLNF-2	2	71.72 + 1.66	76.79 + 1.23	72.22 + 1.15	67.92 + 1.00	42.52 + 1.46	39.22 + 1.24	42.42 + 1.22
SLNF-3	4	74.52 + 1.10	79.82 + 1.33	73.12 + 1.12	69.32 + 1.46	43.32 + 1.55	41.82 + 1.11	43.02 + 1.46
SLNF-4	6	75.28 + 1.10	82.04 + 1.21	76.12 + 1.08	72.62 + 1.57	44.52 + 1.54	43.22 + 1.77	43.72 + 1.25
SLNF-5	8	75.38 + 1.21	82.05 + 1.38	78.82 + 1.46	76.32 + 1.10	45.52 + 1.28	43.82 + 1.34	44.32 + 1.24
SLNF-6	10	75.79 + 1.07	82.82 + 1.24	81.12 + 1.88	78.32 + 1.09	45.52 + 1.06	45.22 + 1.69	46.72 + 1.07
SLNF-7	24	77.75 + 1.88	83.02 + 1.03	81.52 + 1.37	80.62 + 1.29	45.92 + 1.29	50.02 + 1.26	52.52 + 1.35

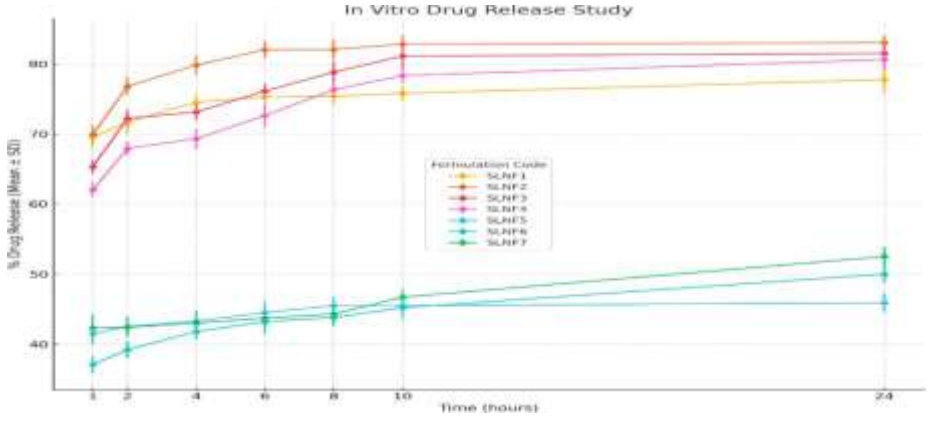

Figure 4. In vitro release study depicting the % Drug release from SLN dispersion

Release kinetic study

The fitting of the obtained release data into different kinetic models provides insights into the drug release mechanisms for each SLN formulation (SLNF-1 to SLNF-7). The regression coefficients (R^2) for each kinetic model help determine which model best describes the drug release behaviour. Zero-order kinetics describes a constant drug release rate. The R^2 values for SLNF-2 (0.9230), SLNF-4 (0.9728), SLNF-5 (0.9975), and SLNF-7 (0.9410) indicate a strong fit, suggesting that these formulations release the drug at a constant rate over time. SLNF-1 also shows a good fit with an R^2 of 0.9128, whereas SLNF-3 (0.7705) and SLNF-6 (0.8234) show moderate fits, indicating less consistent release rates. First-order kinetics describes drug release proportional to the drug concentration remaining in the dosage form. The R^2 values for all formulations are relatively low, with SLNF-2 (0.2929), SLNF-3 (0.3915), SLNF-4 (0.4605), and SLNF-5 (0.2183) showing particularly poor fits. This suggests that first-order kinetics does not adequately describe the release behavior for these formulations. The Higuchi model describes drug release as a diffusion process based on Fick's law. The R^2 values for SLNF-3 (0.9615), SLNF-5 (0.9611), SLNF-6 (0.9295), and SLNF-1 (0.9245) indicate a strong fit, suggesting that diffusion is the predominant mechanism for these formulations. SLNF-2 (0.8576) and SLNF-4 (0.8844) show good fits, while SLNF-7 (0.9121) also indicates a strong diffusion-based release. The Hixson-Crowell model describes drug release with changes in surface area and diameter of particles. The R^2 values are generally low, with SLNF-6 (0.6234) and SLNF-7 (0.5739) showing the highest but still moderate fits. This indicates that the drug release is not predominantly governed by changes in surface area and particle size for most formulations. The Korsmeyer-Peppas model characterizes drug release from polymeric systems and can indicate the release mechanism. SLNF-6 (1.0014) and SLNF-2 (0.9701) show the highest R^2 values, indicating an excellent fit. SLNF-1 (0.9569), SLNF-4 (0.9143), SLNF-5 (0.9631), and SLNF-7 (0.9341) also show strong fits, suggesting a combination of diffusion and erosion mechanisms. SLNF-3 (0.8961) shows a slightly lower but still significant fit.

The analysis indicates that the Zero-Order and Korsmeyer-Peppas models best describe the drug release kinetics for most formulations, particularly SLNF-2, SLNF-4, SLNF-5, and SLNF-7. This suggests that these formulations provide a consistent and controlled release, likely governed by a combination of diffusion and polymer erosion. The Higuchi model also fits well for several formulations, indicating diffusion-driven release. However, the First-Order and Hixson-Crowell models do not adequately describe the release behaviour, suggesting that these mechanisms are less relevant for the studied formulations. Overall, SLNF-2 stands out with high R^2 values across multiple models, indicating its robustness and reliability in providing controlled and predictable drug release. SLNF-1, SLNF-4, and SLNF-5 also show strong performance, making them suitable candidates for consistent drug delivery systems.

Table 4. Fitting of the obtained release data into the different kinetic models

Kinetic models	Regression Coefficient	SLNF-1	SLNF-2	SLNF-3	SLNF-4	SLNF-5	SLNF-6	SLNF-7
Zero order	R^2	0.9128	0.9230	0.7705	0.9728	0.9975	0.8234	0.9410
First order	R^2	0.7652	0.2929	0.3915	0.4605	0.2183	0.4143	0.3888
Higuchi	R^2	0.9245	0.8576	0.9615	0.8844	0.9611	0.9295	0.9121
Hixson Crowell	R^2	0.1955	0.4785	0.5421	0.4431	0.5573	0.6234	0.5739

Korsmeyer Peppas	R^2	0.9569	0.9701	0.8961	0.9143	0.9631	1.0014	0.9341

Surface morphology study

The left image revealed a highly irregular and rough surface with noticeable folds and ridges, suggesting a high degree of surface area. This texture could enhance drug loading capacity and interaction with biological tissues. In contrast, the right image displays a more uniform and smoother surface with some irregularities and small particles, indicating a less complex surface structure. These morphological differences could significantly impact the drug delivery properties of each formulation. The rough surface morphology in the left image could be beneficial for drug delivery systems where high surface area is advantageous for better drug adsorption and release. Overall, these SEM images highlighted how surface morphology can influence the performance of drug delivery systems. The smoother surface could be preferable for controlled and rapid drug release. Further characterization and analysis would be necessary to fully understand the impact of these morphological differences on their drug delivery efficacy.

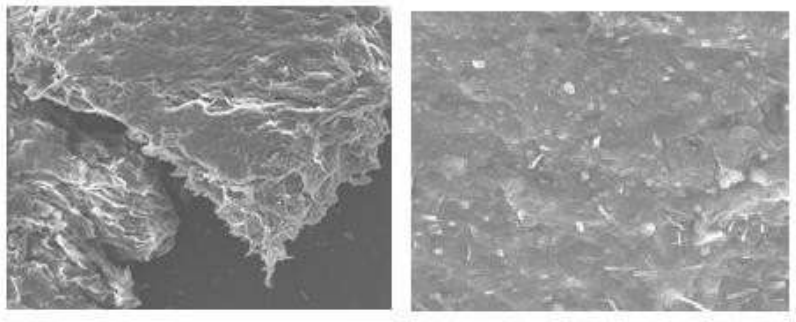

Figure 5. SEM images of SLNF-2 formulation

Drug excipient interaction study: FTIR studies

The pure drug and the SLNF-2 formulation have been compared using FTIR analysis. In the IR spectra of the drugs and the formulation, distinctive peaks corresponding to nitro compounds, alcohols, carboxylic acids, and ethers were detected, notably in the 1000-1500 cm-1 region. The investigation unequivocally showed that there was no meaningful drug-excipient interaction. It was stated that the medication and the excipients used to create the formulation were compatible.

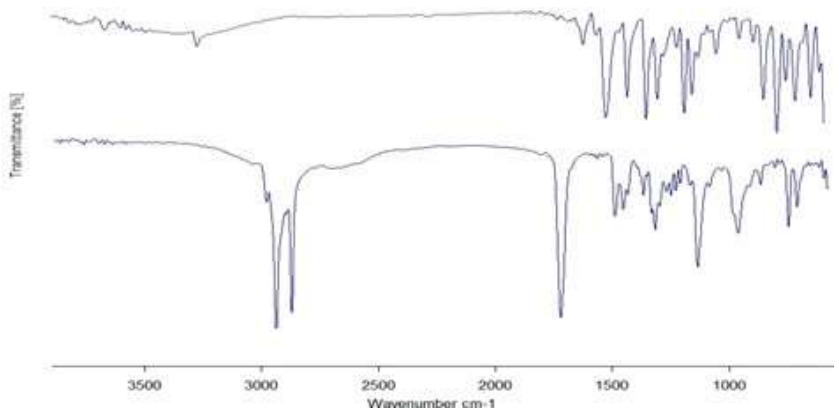

Figure 6. FTIR spectra of the Meloxicam and the SLNF-2 formulation

Fabrication of gel formulation: Incorporation of the SLN into the gel form

For further study, the SLNF-2 with the best values of all the observed parameters was selected. It was added to the gel form by following the previously described process. The subsequent parameters were assessed:

Appearance, homogeneity and Spreadibility of the gel:

Visual inspection revealed a clear, thick, and uniform consistency to the gel. It was translucent and had a silky texture. After calculation, spreadibility (S) was discovered to be 34.81 gm.cm/sec.

Viscosity and Thixotropy of the gel:

The viscosity measurement experiments of the produced gels performed using the Brookfield Viscometer and were found to be are satisfactory Since topical formulations' rheological behaviour is related to their spreadability and duration of contact with the skin, it has been evaluated and the findings including the rheological evaluations indicated that the gel is thixotropic.

Permeation data analysis:

Using the epidermis of pig ears, permeation investigations were conducted with the SLNF-2 gel. The epidermis was prepared in the manner previously described, and parameters including the permeability coefficient (Kp) and steady state flux (Jss) were calculated. Comparing the formulation to the free drug gel formulation, it was discovered that these metrics had greatly risen. This may be due to the lipid and surfactant in the SLN gel formulation, which may improve drug penetration and result in a longer-lasting release of the medication. The permeation studies detailed in Table 5 compare the amount of drug permeated from a free drug gel and an SLN gel over various time points, measured in µg/cm²/hr. Initially, at the 1-hour mark, the free drug gel exhibits a significantly higher permeation rate of 51.98 µg/cm²/hr compared to the SLN gel's 23.98 µg/cm²/hr. This trend continues at 2 hours, with the free drug gel maintaining a higher permeation rate (82.18 µg/cm²/hr) than the SLN gel (60.88 µg/cm²/hr), indicating a quicker initial drug release from the free drug gel. However, the

dynamics change over time. By the 4-hour mark, the SLN gel nearly matches the free drug gel, with permeation rates of 101.25 µg/cm²/hr and 103.32 µg/cm²/hr, respectively. At 8 hours, the SLN gel surpasses the free drug gel, demonstrating a permeation rate of 127.65 µg/cm²/hr compared to 123.96 µg/cm²/hr for the free drug gel. This trend continues at 10 hours, where the SLN gel exhibits a higher permeation rate of 147.07 µg/cm²/hr compared to the free drug gel's 135.40 µg/cm²/hr, underscoring the SLN gel's sustained release capability. By the 24-hour mark, the SLN gel's permeation rate significantly exceeds that of the free drug gel, with values of 157.28 µg/cm²/hr and 137.26 µg/cm²/hr, respectively. This data indicates that while the free drug gel provides a higher initial drug release, the SLN gel ensures a more prolonged and controlled release over time. The SLN gel's ability to maintain a steady and extended drug release suggests it is more effective for applications requiring sustained drug delivery. Consequently, the SLN gel formulation may offer enhanced therapeutic efficacy and improved patient compliance by maintaining therapeutic drug levels over an extended period.

Table 5. The results of the permeation studies

Sl. No	Time (hrs)	Amount of gel (free drug) permeated (µg/cm2/hr)	Amount of SLN gel permeated (µg/cm2/hr)
1	1	51.98 + 0.264	23.98 + 0.121
2	2	82.18 + 0.155	60.88 + 0.353
3	4	103.32 + 0.356	101.25 + 0.244
4	8	123.96 + 0.366	127.65 + 0.575
5	10	135.40 + 0.264	147.07 + 0.263
6	24	137.26 + 0.330	157.28 + 0.155

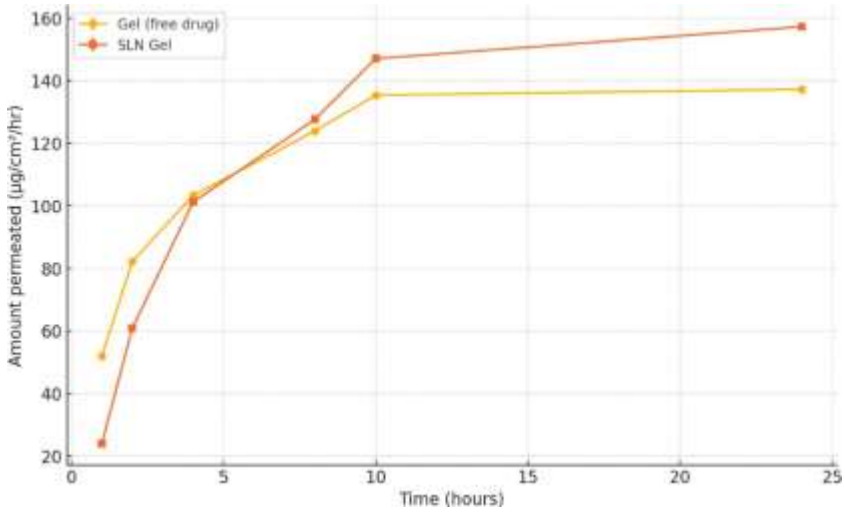

Figure 7. The amount of drug permeated from both the free drug gel and the SLN gel.

4. Conclusions

The study successfully formulated and characterized Meloxicam-loaded solid lipid nanoparticles fabricated into gel formulation (SLNFs), identifying SLNF-2 as the most promising formulation based on its particle size, low polydispersity index, high zeta potential, and superior drug loading and entrapment efficiency. The in vitro release studies demonstrated that SLNF-2 provided a sustained drug release profile, significantly outperforming other

formulations. Kinetic analysis revealed that the release from SLNF-2 followed zero-order and Korsmeyer-Peppas models, indicating a consistent and controlled release mechanism. FTIR and DSC analyses confirmed the absence of significant drug-excipient interactions, ensuring the stability and compatibility of the formulation. The incorporation of SLNF-2 into a gel form further enhanced its application, providing a clear, homogeneous, and thixotropic gel suitable for topical delivery. Permeation studies using pig ear skin confirmed that the SLN gel formulation achieved a more prolonged and controlled release compared to a free drug gel, demonstrating its potential for sustained drug delivery. Overall, the SLN gel formulation of Meloxicam presents a promising approach for enhancing therapeutic efficacy and improving patient compliance in the treatment of inflammatory conditions. Further in vivo studies are warranted to confirm these findings and explore the full potential of this delivery system.

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