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ADVANCEMENTS IN NANOGEL BASED DRUG DELIVERY SYSTEMS: CURCUMIN LOADED FORMULATION FOR IMPROVED MANAGEMENT OF ACUTE PAIN THERAPY

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ABSTRACT:

Curcumin-loaded solid lipid nanoparticles (SLNs) were fabricated using the emulsification-solvent evaporation method. The SLNs exhibited an average particle size of 136.7 ± 8.36 nm, with an entrapment efficiency of 70.83 ± 0.54%. In vitro release studies showed a sustained release profile, with 45.66% of the drug released over 24 hours, indicating prolonged drug delivery compared to curcumin plain gel. In an inflammation model, the formulation demonstrated significant inhibition of edema, with a maximum inhibition of 73.81±0.206% observed after three hours of inflammation induction. Furthermore, when applied 12 hours before carrageenan injection, the formulation exhibited sustained therapeutic action, resulting in 94±0.106% inhibition of edema. Skin irritation studies revealed no significant irritation, suggesting the formulation's safety for topical application. These findings underscore the potential of curcumin-loaded SLNs as an effective strategy for acute pain therapy, offering enhanced stability and sustained therapeutic effects when administered topically.

Keywords: Curcumin, solid lipid nanoparticles, acute pain therapy

Introduction:

Acute pain is a common experience resulting from injury, surgery, or medical conditions and typically serves as a warning signal to the body, indicating tissue damage or potential harm. Effective management of acute pain is crucial not only for the patient's comfort but also for optimizing recovery outcomes and preventing the transition to chronic pain. Acute pain therapy encompasses a range of approaches aimed at promptly alleviating pain and promoting healing. These strategies may include pharmacological interventions, non-pharmacological techniques, and interdisciplinary approaches tailored to the individual's needs and the nature of the acute pain condition [1].

Curcuma longa, commonly known as turmeric, has been extensively studied for its diverse biological properties [2, 3]. It has shown promise in the treatment of various diseases, owing to its anti-inflammatory, antioxidant, anti-cancer, and wound healing effects [4]. However, the therapeutic utilization of curcumin, the active compound in turmeric, faces significant challenges such as photodegradation and low bioavailability [5]. The oral absorption of curcumin is particularly inefficient, hindering its ability to achieve therapeutic efficacy [6]. This is primarily due to its poor absorption, rapid metabolism, and systemic elimination [7].To overcome these limitations, topical administration offers several advantages, including site-specific targeting, bypassing first-pass metabolism, and improved patient compliance [8]. Various formulations have been explored for topical drug delivery, including solid preparations such as topical powders [9,10], liquid formulations like lotions, liniments, emulsions, and suspensions, and semi-solid preparations such as creams, pastes, and gels. Among the novel approaches for enhancing topical delivery, solid lipid nanoparticles (SLNs) have emerged as a promising option. SLNs offer several advantages, including reduced cytotoxicity, a solid matrix that provides chemical protection to the incorporated drug [11], and enhanced adhesive properties to the skin due to the presence of excipients [12, 13]. By encapsulating curcumin within SLNs, its bioavailability and therapeutic efficacy can be improved, thereby potentially overcoming the challenges associated with its oral administration.

Materials and methods

Materials

Curcumin was sourced from Hi Media, India, a reputable supplier known for providing high-quality laboratory reagents and chemicals. Stearic acid, Tween 80, carbopol 940, and ethanol were obtained from Sigma-Aldrich, India, a well-known distributor of analytical-grade chemicals and laboratory supplies. Sigma-Aldrich is recognized for its stringent quality control measures and adherence to international standards, ensuring the reliability and purity of the chemicals procured for research and experimentation purposes.

Methods

Preparation of Nanoparticles

The preparation of curcumin-loaded solid lipid nanoparticles (SLNs) was carried out using a modified emulsion/solvent evaporation method [14]. Initially, the lipophilic material, stearic

acid, was heated above its melting point until it became a liquid. Simultaneously, the aqueous phase containing the surfactant Tween 80 was also heated to the same temperature. Curcumin, the active ingredient, was incorporated into the melted lipid phase, which was then dissolved into the organic solvent ethanol [15]. Subsequently, the organic phase containing curcumin was added dropwise into the hot aqueous phase under vigorous stirring. The resulting dispersion was continuously homogenized for 10 minutes at 12,000 rpm to ensure uniform distribution and optimal encapsulation of curcumin within the SLNs.

The dispersion obtained was subjected to sonication for duration of one hour in a bath sonicator, facilitating the formation of a nanodispersion. Subsequently, the resulting nanodispersion chilled by using ice water maintained at 0°C, leading to the formation of nanoparticles [16].

Table 1: Illustrates the formulation of nanoparticles

Formulationcode	Curcumin(mg)	Stearicacid(mg)	Tween80(ml)	Ethanol(ml)
SL1	20	150	1	10
SL2	20	200	1	10
SL3	20	250	1	10
SL4	20	300	1	10
SL3S1	20	250	0.5	10
SL3S2	20	250	1.5	10
SL3S3	20	250	2	10

Size and Shape

The size and shape of the prepared Solid Lipid Nanoparticles (SLN) were assessed using transmission electron microscopy (TEM). A drop of the sample was deposited onto a copper grid, which was subsequently placed into a desiccator and allowed to dry for 24 hours. Subsequently, the dried sample was examined using a transmission electron microscope.

Zeta potential and polydispersity indices

Zeta potential and polydispersity indices (PDI) were determined using a ZetasizerNanoZS instrument (Malvern Instruments, UK) employing dynamic light scattering. The SLNs were suspended in distilled water and analyzed with the Zetasizer [17].

Entrapment efficiency

The entrapment efficiency of curcumin-loaded solid lipid nanoparticles was assessed by measuring the concentration of unencapsulated drug in the dispersion of solid lipid nanoparticles in methanol. A specified dilution of the SLN dispersion was prepared in methanol and centrifuged at 14,000 rpm for 10 minutes. The resulting filtrate was then analyzed for free unencapsulated curcumin at 423 nm using a validated UV-spectrophotometric method, following appropriate dilution. The quantity of free drug present in the supernatant was then calculated [18].

Entrapment efficiency was calculated by

EE % = ($C_{initial}$ drug – C_{free} drug / $C_{initial}$ drug) × 100

Where $C_{initial}$ is the concentration of initial drug used and C_{free} can be denoted as the concentration of free drug determined in filtrate after centrifugation of methonolic solution.

***In-Vitro* Drug release study**

In vitro drug release from the prepared system was evaluated using an egg membrane as a biological model. The egg membrane was first stabilized in pH 6.8 buffer and then securely fixed in a beaker. The receiver compartment was filled with pH 6.8 buffer as the medium. A predetermined amount of the test formulation was applied onto the donor compartment. At specified time intervals, a 1 ml sample was withdrawn from the receiving compartment and analyzed using UV-visible spectrophotometry. Fresh buffer medium was added as needed to maintain the volume, and the drug content was subsequently estimated.

Stability

For stability assessment, the formulations were stored at three distinct temperature conditions for a duration of 2 months. These temperatures included freezing temperature (approximately 0°C), refrigeration conditions (2°C - 8°C), and room temperature (25°C). The shelf life of the stored systems was determined by monitoring their drug content. Parameters for inspection included observing phase separation and ensuring transparency (absence of any clumps) [19].

Preparation of SLN system into gel

The incorporation of the prepared SLN system into a gel involved formulating SLNs into gels using carbopol 940. A specified quantity of carbopol 940 was dispersed in distilled water to create 1% dispersion. The dispersion was homogenized using a mechanical stirrer for 60 minutes. Subsequently, solid lipid nanoparticles encapsulating the drug were added to formulate the final curcumin-loaded SLN-gel.

Viscosity

The viscosity of the prepared formulation was measured using the Brookfield DV III ultra V6.0 RV cone and plate rheometer (Brookfield Engineering Laboratories, Inc., Middleboro, MA). Spindle # CPE61 was utilized to determine the viscosity of gels at a controlled temperature of 25±0.5°C.

Pharmacodynamic (anti-inflammatory activity by edema inhibition)

The anti-inflammatory activity was assessed using the rat paw edema method, induced by carrageenan in Wistar albino rats, following an experimental procedure approved by the institutional animal ethical committee. The formulations were compared against a positive control, oral curcumin, and a commercial Diclofenac topical gel as a demonstrative reference. Eighteen rats were divided into six groups of six rats each. Initial paw volumes were measured, and treatments were applied according to the following scheme: Group I received oral curcumin (110 mg/kg), Group II received 1 g of marketed diclofenac gel, while Group III received the prepared curcumin-loaded SLN-gel formulation.

Carrageenan suspension (1%) was prepared 1 hour before experimentation, and 0.1 ml was administered into the plantar side of the right hind paw of each rat. Paw volume readings were taken at 1, 2, 3, 4, 5, 6, and 24 hours after carrageenan injection. The sustained effect of the prepared formulation was also evaluated by applying it 24 hours after carrageenan injection and comparing it with the marketed preparation. The untreated paw served as the negative control.

$$\frac{Tc - Tt}{Tc} \times 100$$

Where ***Tc*** represents the measurements paw thickness in the control group and ***Tt*** represents the measurement of paw thickness in the treatment group. The data were represented as mean ± S.E.M statistical significance was determined using ANOVA test with a significance level of P>0.05[20,21]

Skin Irritation Studies

The skin irritation study was conducted on Wistar rats of both sexes, weighing between 150 to 250 grams. The animals were acclimated to standard laboratory conditions prior to the experiment. They were divided into three groups, each containing four animals: Group 1 served as a control group and received no treatment. Group 2 was treated with a standard formulation, specifically the marketed formulation of diclofenac sodium gel. Group 3 was designated as the test group and was treated with the curcumin SLN gel formulation at a dosage of 110 mg/kg. The formulation was topically applied to a shaved surface. The impact of the formulation on rat skin was observed and scored on a scale from 0 to 4 according to the Draize test, assessing erythema, redness, and any allergic reactions [22].

Results:

The particle size of the prepared SLN formulation was influenced by the lipid compositions, with variations observed in each category. Additionally, all surfactant compositions impacted the entrapment efficiency of SLNs. The optimized formulation exhibited particle sizes within the range of 130 - 160 nm, with consecutive size variations noted across different categories. The formulation exhibiting the smallest Polydispersity Index (PDI) observed was 0.316. Furthermore, the surface charge of the formulation, measured by zeta potential, ranged from -10 to -20 mV. Notably, the highest entrapment efficiency is detailed in the table provided.

Tableno2: Physicalcharacterizationofprepared formulation

Code	Particlesize(nm)	PDI	EE%	Zetapotential
SL1	84.93±11.6	0.853±0.112	29.2±0.25	-17.5
SL2	102.3±6.64	0.719±0.412	47.9±0.98	-15.3
SL3	157.7±10.1	0.440±0.312	62.5±0.85	-19.3
SL4	318±15.2	0.518±0.814	56.4±1.5	-19.4
SL5	136.7±8.36	0.316±0.91	70.8±0.54	-20.8
SL6	218.8±19.2	0.518±0.51	69±2.1	-17.6

Note: Alldataarticulated asmean ±S.D.; n=3, allthe experimentsperformedtriplicate

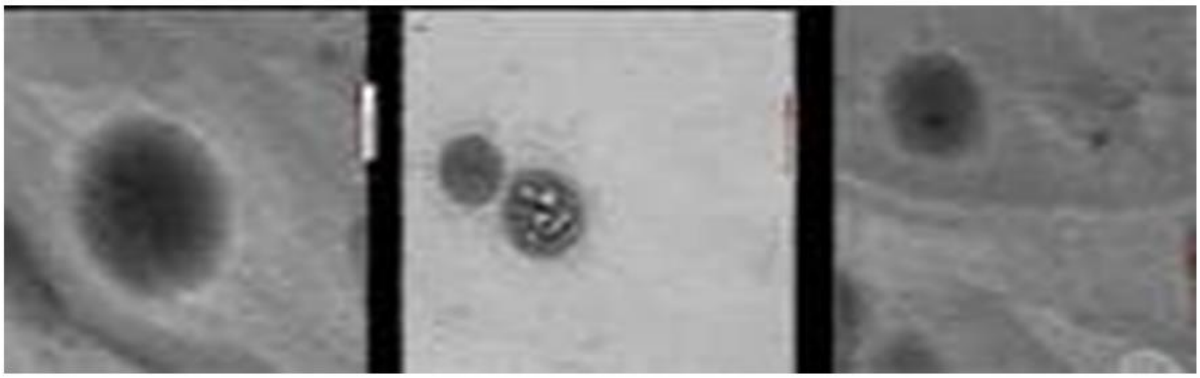
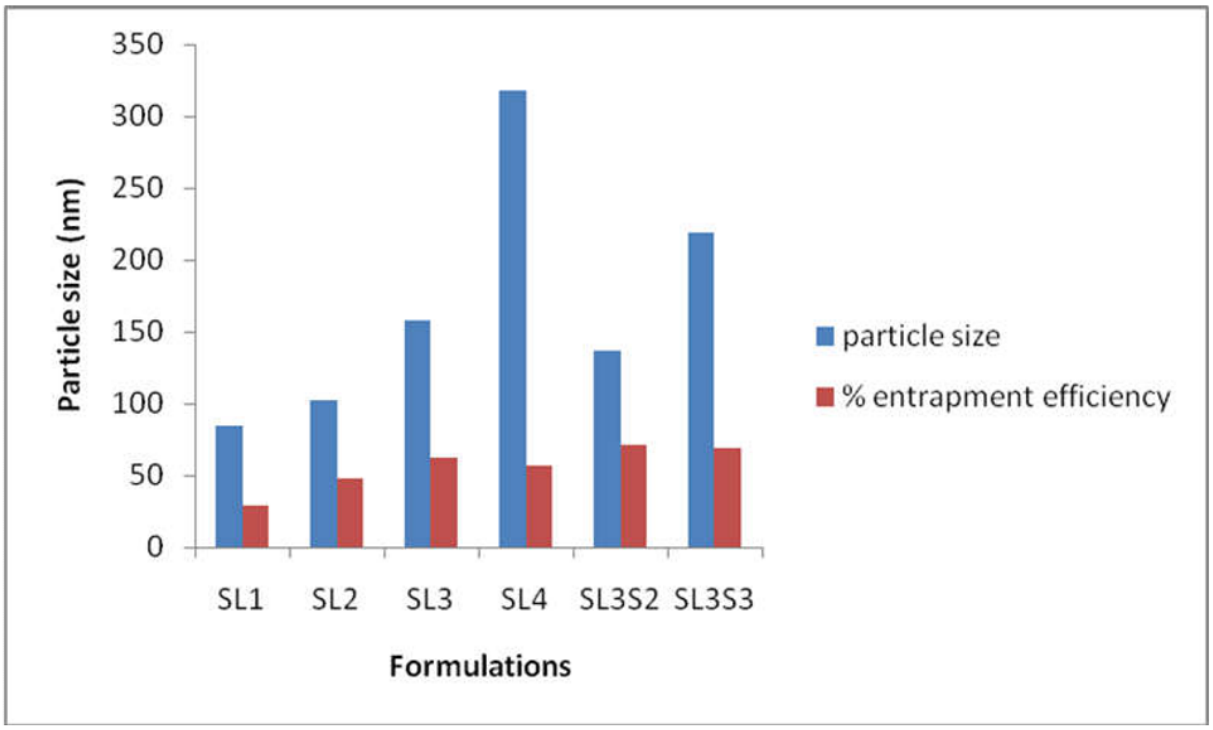


Figure no: 1 TEM images of prepared solid lipid nanoparticles system



Figureno: 2Comparativedataofoptimizationofformulationvariablesanditseffectonparticlesize and entrapment efficiency

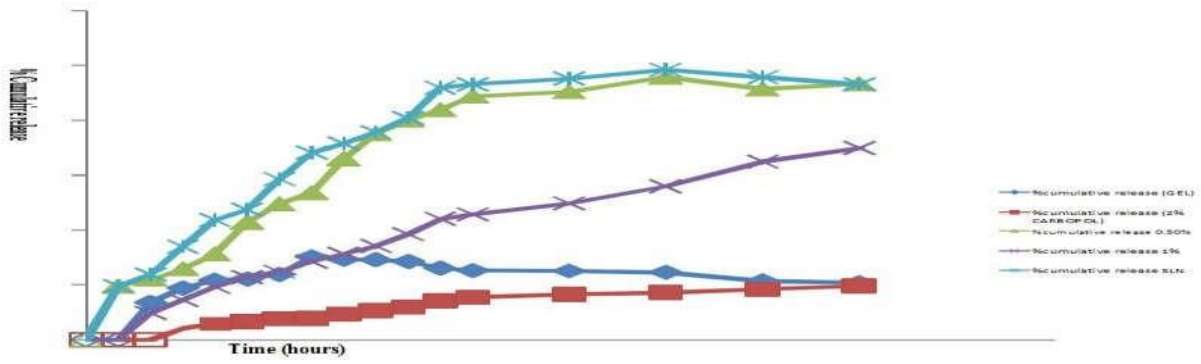
Characterization of Prepared Gel System

The viscosity and Spreadability of various formulations were characterized. The results are presented in Table 3.

Tableno: 3 Characterizationof SLN-gelsystem

CharacterizationofSLN-gelsystem		
Formulation	**Viscosity (Cp)**	**Spreadabilty(cm)**
SL3S1H3S3G1	6213±0.243	4±0.251
SL3S1H1S3G2	11923±1.050	3.5±0.256
SL3S1H1S3G3	23954±0.964	2. 5±0.5

Viscositydeterminedon different compositionsofcarbopolgels.
Note:Alldataarticulated asmean ±S.D.; n=3, allthe experimentsperformedtriplicate



Figureno: 3ReleaseprofilefromdifferentpreparedSLNsystem

In-Vitro drug release

In-vitro drug release profiles from various gel formulations of Solid Lipid Nanoparticles (SLN) were analyzed, as depicted in Figure 2. The incorporation of prepared SLN formulations into gel resulted in a 45.66% drug release over 24 hours. The drug release profile exhibited considerable variability with different polymer concentrations, ranging from 88.80% to 15.46% of drug release when polymer concentrations varied from 0.5% to 2%. Notably, the SLN preparation alone showed a high drug release of 93.18%. In comparison, plain curcumin gel demonstrated a drug release of 25.24% over the same 24-hour period.

Pharmacodynamic (anti-inflammatory activity by edema inhibition)

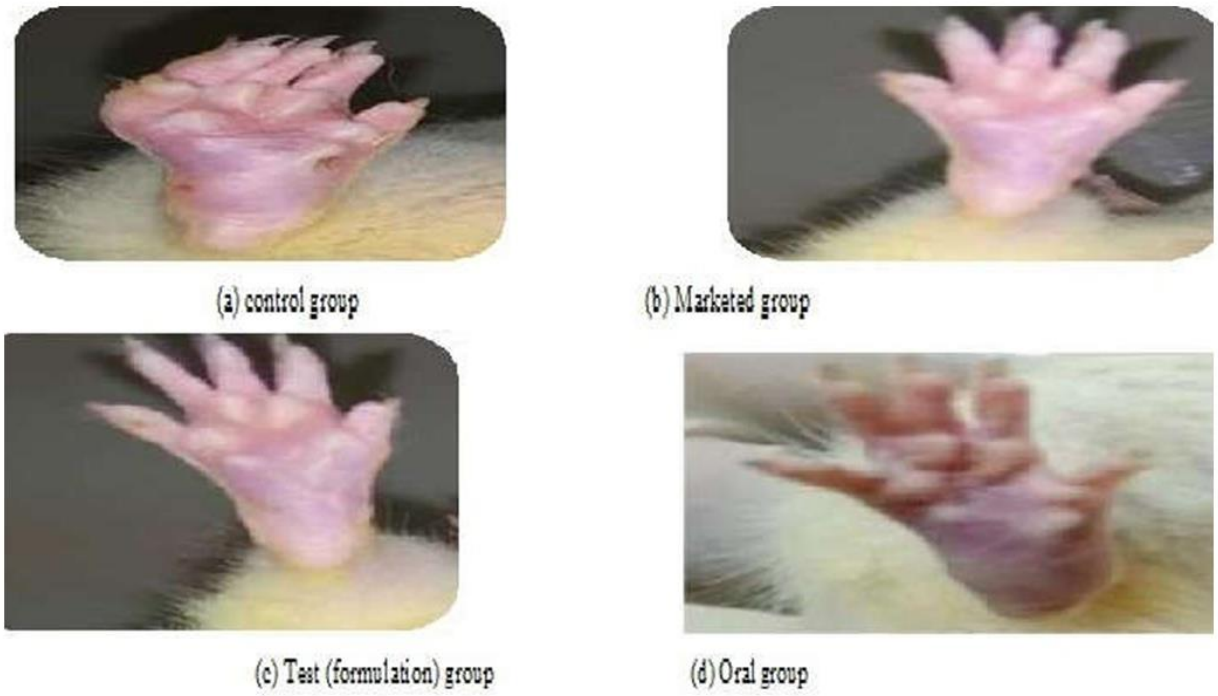
It is evaluated through edema inhibition induced by carrageenan suspension, was conducted using solid lipid nanoparticle (SLN) formulations incorporated into gel. The results demonstrated

superior edema inhibition in the SLN-gel system compared to other groups. Remarkably, the SLN-gel system exhibited a maximum of 70% edema inhibition within a 3-hour timeframe.

Tableno:4Effectofdifferentformulation oncarrageenaninducedpawedema

Group	Treatment	%pawedemainhibitionbydifferentgroups						
		0h	1h	2h	3h	4h	5h	24h
1	Control	---	---	---	---	---	---	---
2	Oral	100±0.16	66.08±0.16	51.08±0.166	56.16±0.1	56.91±0.168	42.72±0.166	27.01±0.1855
3	Standard	100±0.166	68.28±0.166	62.21±0.1452	64.98±0.1997	70.59±0.1855	70.16±0.3	56.22±0.2603
4	Test	100±0.0896	58.78±0.2878	56.69±0.0622	73.81±0.2000	57.77±0.160	58.96±0.2034	36.52±0.077
5	Standard after 12hour	100±0.1666	71.21±0.1766	64.66±0.2111	70.65±0.1887	71.77±0.166	74.32±0.145	93.4±0.166
6	Test(12h after)	100±0.0896	72.42±0.1666	64.21±0.2131	68.11±0.1667	70.34±0.213	75.54±0.1845	94.6±0.166

Note: All data articulated as mean ± S.D.; n = 3, all the experiments performed triplicate



Figureno:4Inflammation inhibitionin ratpaw indifferentgroupsa, b,c andd

Skin Irritation studies

Skin irritation studies were conducted on the prepared solid lipid nanoparticles (SLN). The results indicated no significant signs of irritation attributed to the prepared system. Evaluation was based on monitoring changes in SLN particle size and conducting physical assessments of the gel, including observations for phase separation and homogeneity.

Tableno: 5 StabilitystudiesofSLNon thebasisof theirparticle size

Days forobservation	Stabilitystudies on thebasis of change in particle size		
	0 ˚ctemperature	4-8 ˚ ctemperature	Room temperature
Day-0	136.4±0.435	136.4±0.435	136.4±0.435
Day-15	136.6±0.423	137.2±0.342	138±0.134
Day-30	136.5±0.387	137.9±0.229	139±0.776
Day-45	137±0.221	138.9±0.765	139.6±0.554
Day-60	137.2±0.325	138.2±0.821	141.9±0.128
Day-75	137.2±0.563	139.1±0.791	147±0.198
Day-90	137.5±0.769	139.8±0.962	150±0.875

Note: All data articulated as mean ± S.D.; n = 3, all the experiments performed triplicate

Discussions:

The discussion highlights the potential of curcumin as a promising alternative for treating acute pain therapy due to its direct action on pro-inflammatory cytokines, coupled with its immunomodulatory properties and minimal side effects. The incorporation of curcumin into solid lipid nanoparticles (SLN) offers a solution to stability challenges, particularly when delivered topically in gel form, which is advantageous for targeting the affected area in acute pain therapy.

In this study, curcumin-loaded SLN were prepared using stearic acid and tween 80 as lipid and surfactant, respectively, aiming to enhance the topical absorption of curcumin. Results revealed that varying the concentrations of lipid and surfactant led to the formation of SLN with different particle sizes, influenced by the lipid-surfactant ratio. The stability of these nanoparticles, as indicated by zeta potential, was notably affected by surfactant concentration, with higher concentrations leading to increased stability. Additionally, the entrapment efficiency was primarily influenced by lipid content, showing an increase with higher lipid concentrations.

In-vitro drug release studies demonstrated that the concentration of the gelling agent affected drug release rates, with higher polymer concentrations resulting in slower release rates. The

formulations developed in this study involved the incorporation of curcumin-loaded SLN into gel for transdermal delivery, filling the gap in the market for curcumin transdermal formulations. Comparative analysis against a commercial transdermal anti-inflammatory gel, Diclofenac topical gel, revealed significant anti-inflammatory effects of the prepared formulations, as demonstrated in the results.

Overall, the findings underscore the potential of curcumin-loaded SLN in gel form for transdermal delivery as a promising approach for acute pain therapy. The study provides valuable insights into the formulation parameters influencing nanoparticle characteristics and highlights the efficacy of the developed formulations in comparison to existing commercial options.

Conclusion:

The physical and chemical characteristics of the gel of solid lipid nanoparticles loaded with curcumin were assessed. The investigation showed that the concentration of surfactant and lipid had a significant impact on the physicochemical characteristics.

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