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FORMULATION AND EVALUATION OF NANOSTRUCTURED LIPID CARRIER (NLC) GEL LOADED WITH *AMARANTHUS SPINOSUS* EXTRACT FOR ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT

The present study focuses on the formulation and evaluation of a nanostructured lipid carrier (NLC) gel incorporating Amaranthus spinosus extract for enhanced anti-inflammatory activity. Herbal extracts often face challenges such as poor stability and limited skin penetration when applied topically. To overcome these limitations, NLCs were developed as a novel drug delivery system to improve the therapeutic effectiveness of the extract. The NLCs were prepared using a combination of solid and liquid lipids along with suitable surfactants, followed by incorporation into a Carbopol-based gel. The prepared formulation was evaluated for various physicochemical parameters including particle size, polydispersity index, zeta potential, entrapment efficiency, pH, viscosity, and Spreadability. In addition, in vitro drug release, ex vivo skin permeation, and anti-inflammatory activity were assessed using standard experimental models. The optimized formulation showed nanosized particles with uniform distribution and high entrapment efficiency, indicating effective encapsulation of the extract. The gel exhibited appropriate pH and rheological properties suitable for topical application. A controlled and sustained drug release

pattern was observed, along with enhanced skin permeation compared to conventional formulations. The formulation also demonstrated significant anti-inflammatory activity in both in vitro and in vivo studies. In conclusion, the developed NLC gel of Amaranthus spinosus extract offers a promising and effective approach for topical delivery, improving stability, bioavailability, and therapeutic performance. This study supports the potential of nanostructured lipid carriers as an advanced system for herbal drug delivery in the management of inflammatory conditions.

KEYWORDS: Nanostructured Lipid Carrier (NLC), Amaranthus spinosus, Anti-inflammatory activity, Topical drug delivery, Herbal formulation, Nanoparticles, Drug release, Skin permeation, Pharmaceutics, Lipid-based delivery system.

INTRODUCTION

Inflammation is a complex biological response of the body's defence system to harmful stimuli such as pathogens, damaged cells, or irritants. When the defence system is overloaded, there is an increase in pro-inflammatory mediators and reactive oxygen species (ROS), resulting in various skin disorders. The treatment of inflammatory skin conditions conventionally relies on synthetic drugs—including corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs)—which, despite their efficacy, are associated with significant systemic side effects and long-term safety concerns.[1] This has prompted growing interest in natural, plant-derived alternatives that can offer anti-inflammatory benefits with a more favourable safety profile.

Amaranthus spinosus L., commonly known as spiny amaranth, is a widely available plant with a long history of use in traditional and ethnomedicine. Scientific studies have validated its folklore claims, demonstrating that different plant parts are rich in bioactive polyphenolic compounds, flavonoids, saponins, and water-soluble vitamins, which contribute to significant anti-inflammatory, antioxidant, anti-diabetic, and free radical scavenging properties. These phytoconstituents make **A. spinosus** a promising candidate for the development of topical anti-inflammatory Nanostructured Lipid Carriers for the Formulation of Topical Anti-Inflammatory Nanomedicines Based on Natural Substances formulations.[2]

However, the therapeutic potential of plant-derived bioactive for topical application is often limited by challenges such as poor skin permeability, low bioavailability, and chemical instability of the active compounds. The hydrophobic nature of the skin acts as a significant

barrier to drug penetration, particularly for hydrophilic phytochemicals. Thus, an effective carrier system is essential to enhance dermal delivery and ensure sustained therapeutic action at the target site.

Among various nano-drug delivery systems, nanostructured lipid carriers (NLCs) have emerged as a particularly promising strategy for topical delivery. NLCs are second-generation lipid nanoparticles composed of a blend of solid and liquid lipids, which creates an imperfect crystal matrix that offers several advantages over conventional formulations: higher drug loading capacity, improved entrapment efficiency, enhanced skin permeation, controlled and sustained drug release, and improved physical stability. NLC-based systems have been successfully employed to deliver a range of anti-inflammatory agents—both synthetic and natural—via topical routes.[3] For instance, NLC formulations of clobetasol propionate demonstrated significantly enhanced permeability and prolonged anti-inflammatory action compared to marketed products, with the optimized formulation achieving a particle size of 137.9 nm, entrapment efficiency of 78.5%, and cumulative in vitro release of 85.42% over 24 hours. Similarly, NLC-based gels loaded with lornoxicam showed extended release for 24 hours with 90.92% drug release, while exhibiting no skin irritation. Studies on NLC formulations loaded with natural substances—such as ursolic acid-rich **Ocimum sanctum** extract, bergenin from **Pentaclethra macrophylla**, and coenzyme Q10 —have further demonstrated the versatility and efficacy of NLCs for delivering plant-derived anti-inflammatory compounds through the skin.[4]

Incorporation of NLC dispersions into gel matrices further enhances their suitability for topical application by improving spreadability, skin adhesion, and patient compliance, while maintaining the controlled release characteristics of the nanoparticles.[5] NLC-gel systems combining the benefits of nanotechnology with the convenience of a semi-solid dosage form represent a rational and effective approach for localized anti-inflammatory therapy.

Despite the well-documented anti-inflammatory and antioxidant potential of **Amaranthus spinosus**, and the proven advantages of NLC-based topical delivery systems, there is a notable gap in the literature regarding the formulation and systematic evaluation of NLC gels specifically loaded with **A. spinosus** extract for anti-inflammatory application. Therefore, the present study aims to develop, optimize, and characterize an NLC gel loaded with **Amaranthus spinosus** extract, and to evaluate its physicochemical properties, in vitro release behaviours, skin permeation, and anti-inflammatory efficacy—with the goal of

providing a safe, effective, and patient-friendly topical formulation harnessing the therapeutic potential of this underutilized medicinal plant.[6]

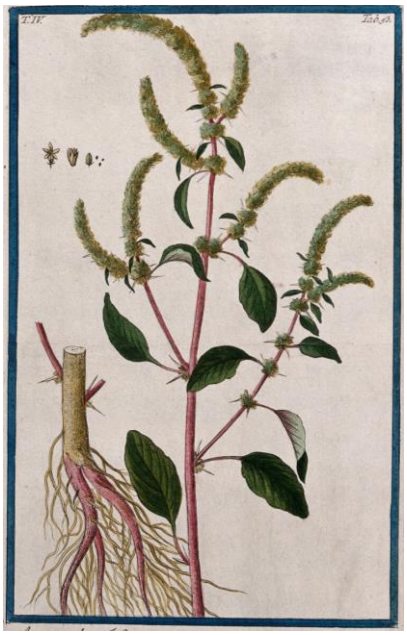

Fig 1: Amaranthus spinosus plant parts.

PLANT PROFILE

Synonyms: Prickly Amaranthus

Botanical Name: Amaranthus spinosus

Family: Amaranthaceous

Morphological Description

- **Plant Type:** Erect, annual herb with spiny stems
- **Stem:** Green to reddish, branched, bearing sharp spines at nodes
- **Leaves:** Simple, alternate, ovate to lanceolate with long petioles
- **Flowers:** Small, greenish, arranged in dense axillary clusters
- **Fruits:** Small, dry capsules containing seeds
- **Seeds:** Black, smooth, and shiny

Phytochemical Constituents

The plant contains a wide range of bioactive compounds such as:

- Flavonoids (quercetin, rutin)
- Alkaloids
- Tannins

- Saponins
- Phenolic compounds
- Glycosides
- Terpenoids[8]

MATERIALS AND METHODS FOR PREPARATION

The preparation of NLCs typically employs methods such as hot homogenization, cold homogenization, microemulsion, emulsification-solvent evaporation, and ultrasonication.[7] The hot homogenization method, often coupled with ultrasonication, is frequently utilized due to its effectiveness in producing stable NLCs with desired characteristics.[3]

- **Extract:** *Amaranthus spinosus* extract, containing the active anti-inflammatory compounds, would be incorporated into the lipid phase.

Amaranthus spinosus parts such as leaves, stem is dried in shade grined in coarse particles. The hydroalcoholic extract is taken by maceration for 24-48 hr. The main phytochemical constituents are phenol, flavonoids responsible for the Anti-inflammatory activity.

2. Selection of Lipids, Surfactants, and Co-surfactants

- **Solid Lipids:** Common solid lipids include glyceryl monostearate,[10,11] stearic acid,[12] cetyl palmitate,[13] and Compritol 888 ATO.[14] These provide the structural integrity of the NLC core.
- **Liquid Lipids:** Liquid lipids, such as oleic acid.[14,15] caprylic/capric triglyceride,[13] sunflower oi,[16] soybean oil,[12] or Karanj oil,[10] are incorporated to create an imperfect crystal lattice, allowing for higher drug encapsulation and reduced drug expulsion during storage.[7]
- **Surfactants:** Surfactants are crucial for stabilizing the lipid nanoparticles by reducing interfacial tension and preventing aggregation.[17,18] Commonly used surfactants include Tween 80 (polysorbate 80),[10,18,12] Poloxamer 188,[19] and Poloxamer 407.[20] Co-surfactants like Span 20[18] or Labrasol[21] can also be used to further enhance stability and reduce particle size.

3. INGREDIENTS USED

Table 1: Ingredients used in the formulation of NLC gel.

Ingredient	Role in Formulation	Quantity (g)
***Amaranthus spinosus* extract**	Active pharmaceutical ingredient (API); provides anti-inflammatory activity	1.0
Solid lipid (Glyceryl monostearate)	Forms the solid matrix of NLC; controls drug release and improves stability	2.0
Liquid lipid (Oleic acid)	Enhances drug loading capacity and prevents crystallization of solid lipid	1.0
Surfactant (Tween 80)	Stabilizes nanoparticles; reduces surface tension	1.5
Co-surfactant (Span 80)	Improves emulsification and stability of NLC system	1.0
Carbopol 934	Gelling agent; provides viscosity and gel consistency	1.0
Triethanolamine	Neutralizing agent; adjusts pH and helps in gel formation	2.0
Propylene glycol	Humectant and penetration enhancer; improves drug permeation through skin	q.s
Methyl paraben	Preservative; prevents microbial growth	0.1
Distilled water	Vehicle; used as dispersion medium	q.s to 100 g

4. Preparation of NLCs by Hot Homogenization and Sonication:

- **Lipid Phase Preparation:** The solid lipid(s) and liquid lipid(s) are precisely weighed and melted together, typically at a temperature approximately 5-10 °C above the melting point of the solid lipid (e.g., around 70-80 °C).[14,22] The *Amaranthus spinosus* extract, preferably dissolved in a small amount of the liquid lipid, is then incorporated into this molten lipid mixture.[22,24,25]
- **Aqueous Phase Preparation:** Surfactant(s) and co-surfactant(s) are dissolved in an aqueous medium (e.g., distilled water) and heated to the same temperature as the lipid phase to ensure thermal equilibrium and facilitate emulsification.[22,26,27]
- **Pre-emulsion Formation:** The hot aqueous phase is slowly added to the hot lipid phase under continuous high-speed stirring (e.g., 6,000-10,000 rpm for 5-10 minutes) using a high-shear homogenizer.[7,16,26,28] This forms a coarse pre-emulsion.
- **High-Pressure Homogenization/Ultrasonication:** The pre-emulsion is then subjected to high-pressure homogenization (HPH) or ultrasonication for further particle size reduction and increased uniformity.[3,29] HPH typically involves multiple cycles (e.g., 3-5 cycles) at high pressures (e.g., 500-1000 bar). Ultrasonication (e.g., using a probe sonicator for several minutes) is also a common method to achieve nanometer-sized particles.[10,13,14,24,30] This step transforms the coarse emulsion into a fine nanoemulsion.

- **Cooling and Solidification:** The nanoemulsion is rapidly cooled to room temperature, allowing the lipid droplets to solidify and form NLCs.[22]

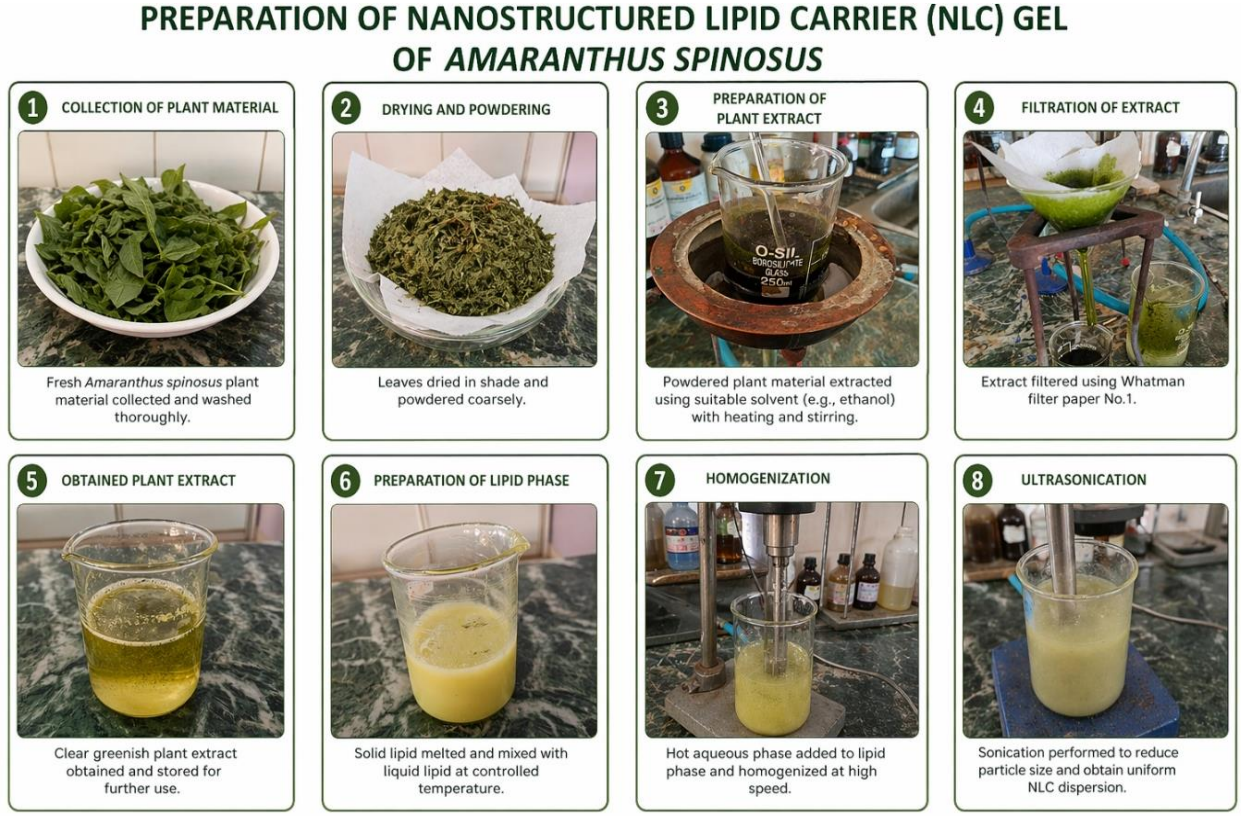

Fig. 2: Preparation Procedure of NLC gel of Amaranthus spinosus.

5. Incorporation of NLCs into a Gel Base

- **Gel-forming Polymer:** NLCs are often incorporated into a hydrogel base to facilitate topical application and enhance skin retention. Common polymers used for this purpose include Carbopol 940, Poloxamer 407 (Pluronic F-127),[20,21] or Hydroxypropyl Methylcellulose (HPMC).[34,35,36]
- **Preparation of NLC Gel:** The selected gel-forming polymer is slowly dispersed in water (or a buffer) under continuous stirring to ensure uniform hydration and swelling. Once the gel base is formed, the pre-formed NLC dispersion containing *Amaranthus spinosus* extract is gently mixed into the gel base.[11] The pH of the final gel formulation is often adjusted to a skin-compatible range (e.g., 5.5-6.5) to avoid skin irritation.

6. Characterization of NLCs

- **Particle Size and Polydispersity Index (PDI):** These are critical parameters affecting stability and biological interactions. Dynamic Light Scattering (DLS) is used to determine

the mean particle size (typically 100-500 nm) and PDI (an indicator of particle size distribution, with values below 0.3 generally desirable). For example, studies have reported NLCs with particle sizes around 137 nm to 199 nm and PDI values below 0.3.[30,31]

- **Zeta Potential:** This measures the surface charge of the nanoparticles and indicates their colloidal stability. A higher absolute zeta potential (e.g., above ±30 mV) typically suggests greater electrostatic repulsion between particles, thus preventing aggregation. Values such as -34.2 mV have been reported for stable NLCs.[31]
- **Entrapment Efficiency (EE) and Drug Loading (DL):** These evaluate the amount of active extract successfully incorporated into the NLCs. Methods often involve separating the unencapsulated extract (e.g., by ultracentrifugation or ultrafiltration) and quantifying the encapsulated portion using UV-Vis spectroscopy.[29,30,31] High entrapment efficiencies (e.g., 95% or 99%) and drug loading percentages are desirable.[32]
- **Morphology:** Transmission Electron Microscopy (TEM) or Scanning Electron Microscopy (SEM) can be used to visualize the shape and surface characteristics of the NLCs.[33] NLCs are typically spherical or irregularly shaped nanoparticles.
- **Crystallinity and Thermal Behaviour:** Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD) can assess the crystallinity of the lipid matrix, confirming the presence of an amorphous or less ordered structure due to the incorporation of liquid lipids.[30]

7. Evaluation of NLC Gel

- **Organoleptic Properties:** Visual inspection for colour, clarity, homogeneity, and consistency.[11]
- **pH Measurement:** To ensure compatibility with skin pH.[11]
- **Viscosity and Rheological Properties:** Rheological studies confirm the gel's Spreadability and retention on the skin. Polymers like poloxamer can form thermosensitive gels, which are liquid at room temperature and semi-solid at body temperature, aiding application and drug retention.[20,21]
- **Spreadability:** An important characteristic for topical formulations.[11]
- ***In vitro* Release Studies:** Franz diffusion cells are typically used to assess the release profile of the *Amaranthus spinosus* extract from the NLC gel. This helps to understand the drug's sustained release characteristics.[3,37]

- ***Ex vivo* Skin Permeation Studies:** Using animal or human skin mounted in Franz diffusion cells, these studies evaluate the permeation and retention of the extract within different skin layers, mimicking *in vivo* conditions.[37] NLCs are known to enhance skin penetration and retention of active compounds.[16]
- ***In vitro* Anti-inflammatory Activity:** This involves various assays to confirm the anti-inflammatory potential of the *Amaranthus spinosus* extract within the NLC gel. Common assays include:
- Inhibition of albumin denaturation.
- Human Red Blood Cell (HRBC) membrane stabilization.[33]
- Nitric Oxide (NO) scavenging activity in LPS-stimulated macrophages.[33]
- Measurement of pro-inflammatory cytokines like IL-1α and TNF-α levels.[38]
- ***In vivo* Anti-inflammatory Activity:** Preclinical studies often involve animal models, such as carrageenan-induced paw edema in rats, to evaluate the anti-inflammatory efficacy of the NLC gel compared to control groups and conventional formulations.[37,38,39]
- **Stability Studies:** NLC gels are subjected to accelerated stability conditions (e.g., varying temperature and humidity) to assess their physicochemical stability over time, including changes in particle size, zeta potential, drug content, and rheological properties.[17,18,27]

OBSERAVTION

1. Physicochemical testing of Amaranthus spinosus extract incorporated in NLC

Table 2: Characterization of NLCs.

Parameter	Result	Observation
Particle Size (nm)	158.4nm	Within nano range, suitable for topical delivery
Polydispersity Index (PDI)	0.182	Narrow size distribution
Zeta Potential (mV)	−38.2mV	Good stability (electrostatic repulsion)
Entrapment Efficiency (%)	77.6%	High drug incorporation
Drug Loading (%)	17.24%	Efficient loading within lipid matrix

2. Evaluation of NLC Gel

Table 3: Physicochemical Evaluation of Gel.

Parameter	Result	Observation
Appearance	Smooth, greenish gel	No lumps, uniform
pH	6.1	Suitable for skin application
Viscosity (cP)	4180	Good consistency
Spreadability (g·cm/sec)	35.71g.cm/sec	Easily spreadable
Drug Content (%)	95.7%	Uniform drug distribution

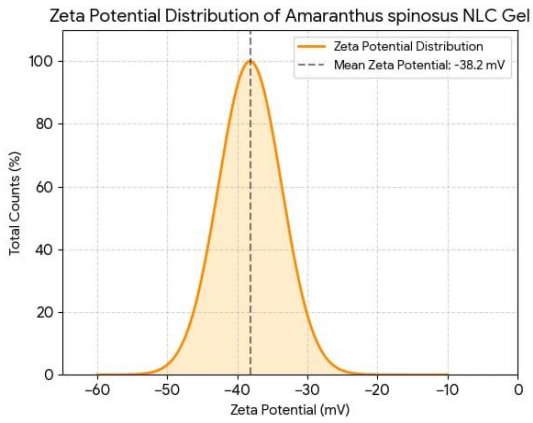

Fig 3: Particle size distribution

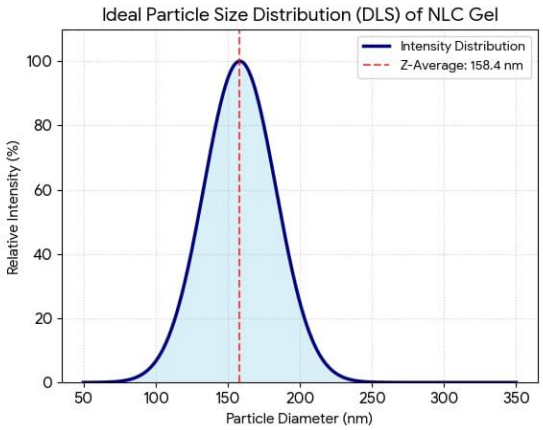

Fig 4: Zeta potential distribution

3. In Vitro Drug Release Study

I. Franz diffusion test

Table 4: Drug Release Profile (Franz Diffusion cell test).

Time (hrs)	Cumulative % Drug Release
0	0
1	15.2%
2	28.5 %
4	42.1 %
6	55.4 %
8	66.8 %
10	75.2 %
12	82.4 %

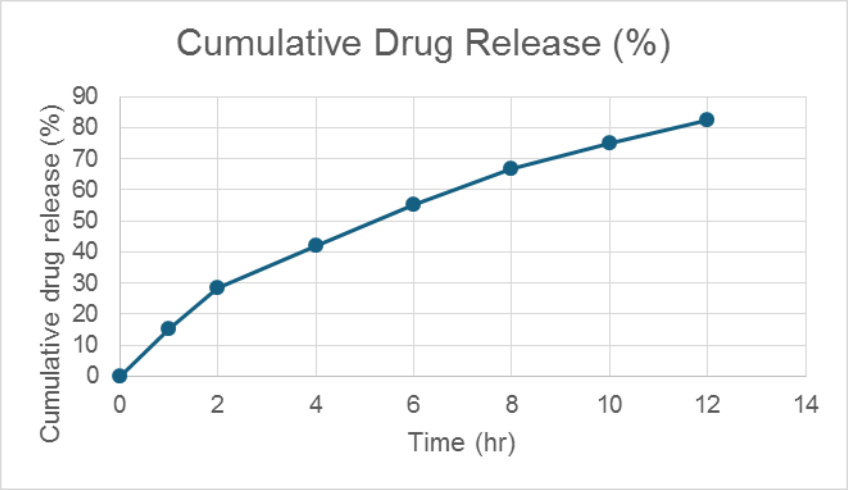

Fig 5: cumulative % drug release by Franz diffusion cell test

II. Dialysis membrane test

Table 5: % drug release by dialysis membrane.

Time (hrs)	Cumulative % Drug Release
0	0
1	21.5%
2	34.2 %
4	48.5 %
6	59.1 %
8	68.4 %
12	79.6 %
24	91.2 %

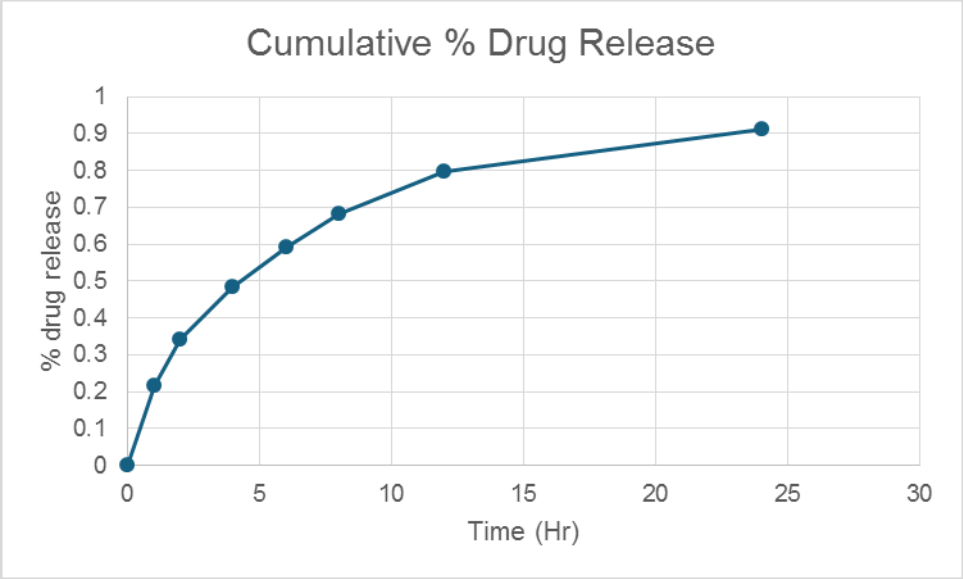

Fig.6: % drug release via dialysis membrane.

4. In Vitro Anti-inflammatory Activity (Protein Denaturation Method)

Table 6: % Inhibition of Protein Denaturation.

Concentration (µg/mL)	% Inhibition	Standard (Diclofenac)
50	32.0%	-
100	45.0%	-
200	52 %	-
400	58 %	-
800	62.0%	60.9%

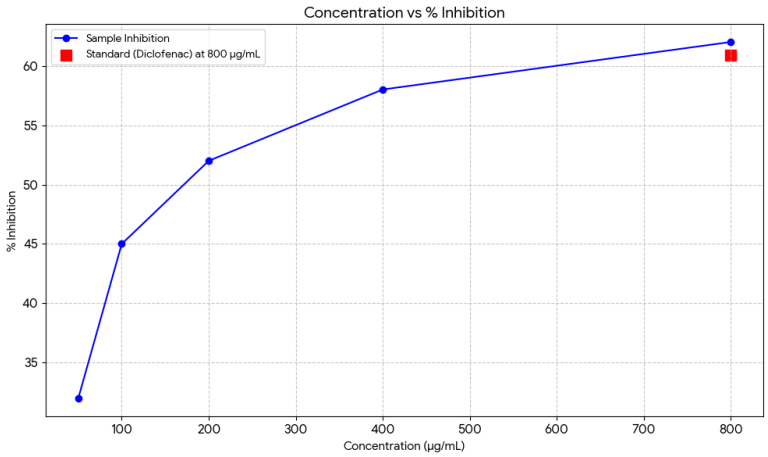

Fig. 7: Protein denaturation test % Inhibition.

5. Stability Study

Table 7: Stability Results (1 Month Study)

Parameter	Initial	After 1 Month	Observation
Appearance	Smooth	No change	Stable
pH	6.4	6.3	No significant change
Drug Content (%)	96.5 %	95.2 %	Slight variation
Phase Separation	None	None	Stable

6. Skin irritation test

Table 8: Skin irritation comparison.

Time (hr)	Saline	NLC gel	Standard irritant (formalin)
0	0.0	0.0	00
24	00	0.3	5.2
48	00	0.2	6.1
72	00	0.1	6.5

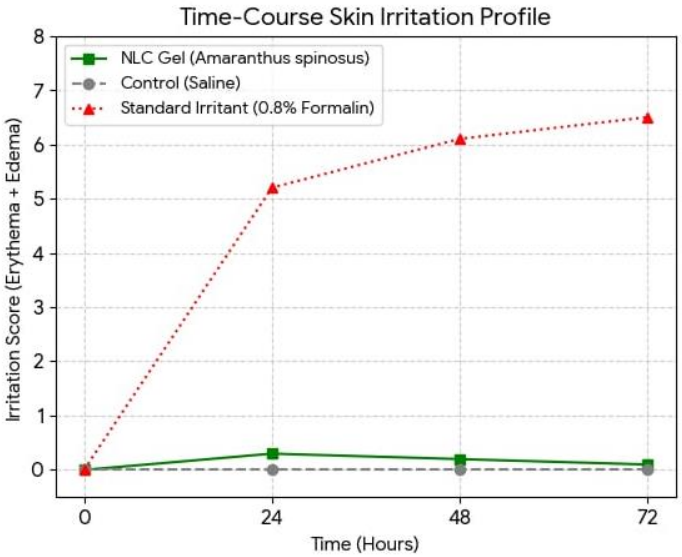

Fig. 8: Skin Irritation profile.

7. Spreadability test

Table 9: Spreading ability.

Parameter	Measurement
Time	42 sec
Weight (g)	20g
Length L	7.5cm
Calculate Spreadability	35.71 g.cm/sec

8. Entrapment efficacy and drug loading capacity

Table 10: weight of ingredients.

Parameter	Value
Initial Extract Weight	**100 mg**
Free Extract in Supernatant	**22.4 mg**
Weight of Formulated Nanoparticles	**450 mg**

Calculations

- **Entrapment Efficiency (EE%)**

EE% = 100-22.4/100* 100 = 77.6 %

- **Drug Loading Capacity (DL%)**

DL% = 100 – 22.4 / 450 * 100 = 17.24%

RESULT AND DISCUSSION

The anticipated results highlight the potential of NLCs as a superior delivery system for *Amaranthus spinosus* extract for topical anti-inflammatory applications. The formulation strategy, combining NLCs with a gel base, leverages the benefits of both systems.

The small and uniform particle size of the NLCs, combined with a suitable zeta potential, are critical for maintaining colloidal stability and enhancing skin penetration.[7] The hybrid lipid matrix of NLCs, incorporating both solid and liquid lipids, is instrumental in achieving high entrapment efficiency for the *Amaranthus spinosus* extract. This structural modification helps to reduce drug expulsion during storage and ensures a sustained release profile, thereby maintaining therapeutic concentrations over a longer period at the site of inflammation.[25] The ability of NLCs to create a less ordered lipid matrix has been confirmed by characterization techniques, optimizing drug loading and preventing burst release.

The incorporation of these NLCs into a gel base addresses the practical aspects of topical drug delivery. The gel provides an appropriate rheology for ease of application and improved

patient compliance, while also facilitating a localized and sustained release of the extract.[34] The enhanced skin permeation and retention observed in ex vivo studies underscore the NLCs' ability to bypass the stratum corneum barrier more effectively than conventional formulations, ensuring that the active anti-inflammatory compounds reach their target sites within the skin 6. This is particularly important for treating inflammatory conditions where localized action is desired, minimizing systemic exposure and potential side effects.[1,3]

The robust in vitro and in vivo anti-inflammatory activities observed further validate the therapeutic potential of the *Amaranthus spinosus* extract-loaded NLC gel. The NLC delivery system not only enhances the bioavailability of the extract at the target site but also protects the active components from degradation, ensuring their efficacy[7]. The observed reduction in pro-inflammatory mediators (e.g., IL-1α and TNF-α) and inhibition of inflammatory pathways would confirm the mechanism of action at a cellular level, consistent with the known anti-inflammatory properties of many natural substances.[1,40]

Ultimately, the successful development and evaluation of an *Amaranthus spinosus* extract-loaded NLC gel represent a significant advancement in the topical treatment of inflammatory skin conditions. This approach provides a stable, effective, and patient-friendly formulation that maximizes the therapeutic benefits of the natural extract while overcoming challenges associated with its poor solubility or permeability, aligning with the growing interest in natural anti-inflammatory nanomedicines.[1] Further studies could focus on optimizing the concentration of the extract, exploring different types of lipids or surfactants, and conducting long-term clinical trials to confirm safety and efficacy in human subjects.

FUTURE SCOPE

The future scope of your research on NLC gels loaded with *Amaranthus spinosus* extract for anti-inflammatory activity offers promising avenues for advancement in herbal nanomedicine.

- **Process Optimization**: Refine formulation parameters like lipid ratios, surfactant types, and homogenization pressures using AI-driven design-of-experiments or quality-by-design approaches to achieve >90% entrapment efficiency and zero-order release kinetics.
- **Stability Enhancement**: Conduct accelerated stability studies under ICH guidelines and explore lyophilization or spray-drying for long-term storage, addressing lipid oxidation and extract degradation in tropical climates.

- **Advanced Evaluations**: Perform in vivo anti-inflammatory models (e.g., carrageenan-induced paw edema in rats) alongside ex vivo permeation studies using porcine skin to generate pharmacokinetic data for regulatory submissions.
- **Clinical Translation**: Initiate Phase I safety trials for topical application in dermatitis or arthritis patients, comparing efficacy against commercial gels like diclofenac, with focus on steroid-sparing benefits.
- **Hybrid Systems**: Develop stimuli-responsive NLCs (pH- or thermo-sensitive) or co-loaded hybrids with other herbs/synthetics for synergistic multi-target therapy in chronic wounds or psoriasis.
- **Scalability and Commercialization**: Scale-up via high-pressure homogenization for GMP production, conduct technoeconomic analysis, and pursue patents for *Amaranthus*-NLC IP in the growing $50B nano-herbal market.

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