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RESEARCH ARTICLE
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NANOSTRUCTURED LIPID CARRIERS: A NEXT-GENERATION LIPID-BASED DELIVERY SYSTEM

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Abstract:
Background: Nanostructured Lipid Carriers (NLCs) are advanced lipid-based nanocarriers developed to address the limitations of Solid Lipid Nanoparticles (SLNs), such as low drug loading and drug expulsion during storage. The inclusion of both solid and liquid lipids in NLCs leads to a disordered internal matrix either imperfect or amorphous enhancing drug entrapment, stability, and enabling controlled drug release.
Objectives: This review aims to evaluate the classification, composition, preparation methods, and pharmaceutical potential of NLCs. It emphasizes structural types (imperfect, amorphous, and multiple-type NLCs), their critical components (solid lipids, liquid lipids, surfactants), and their mechanisms for improving drug delivery and bioavailability.
Methodology: A literature-based analysis is conducted to review various formulation strategies and preparation techniques for NLCs. Key physicochemical parameters such as particle size, polydispersity index (PDI), zeta potential, and drug encapsulation efficiency are discussed in terms of their impact on formulation performance.
Expected Outcomes: NLCs are shown to enhance bioavailability through improved solubility, increased permeability across skin and mucosal barriers, and lymphatic uptake. Their biodegradability, scalability, and ability to support site-specific delivery make them suitable for oral, topical, transdermal routes.
Conclusion: NLCs offer significant potential as next-generation drug delivery systems. While challenges such as cytotoxicity and surfactant-related hypersensitivity exist, ongoing innovations in lipid selection and formulation highlight their growing role in advancing pharmaceutical delivery for a wide range of therapeutic agents.

Keywords: Nanosystem, Stability, Drug Entrapment, Bioavailability, Drug delivery

Introduction:

Nanomedicine has witnessed significant advancements in recent years, leading to the development of various nanocarrier systems aimed at optimizing drug delivery. These systems are broadly categorized into polymeric and lipid-based platforms(1). Polymeric nanosystems include nanocapsules, nanospheres, nanofibers, and nanodiscs, while lipid-based carriers encompass

liposomes, transferosomes, ethosomes, niosomes, virosomes, phytosomes, micelles, solid lipid nanoparticles (SLNs), and the more advanced nanostructured lipid carriers (NLCs)(2). SLNs were initially introduced in the early 1990s as colloidal carriers employing physiological lipids, offering significant advantages such as biocompatibility and reduced systemic toxicity . However, SLNs faced limitations like poor drug loading capacity and drug expulsion during storage. To address these challenges, NLCs were developed as a second-generation lipid-based system, comprising both solid and liquid lipids in their matrix .NLCs are nanometric, multiparticulate carriers typically ranging from 50 to 500 nanometers in diameter(3). Their particle size and polydispersity are significantly influenced by the formulation components and production methods employed (4) These carriers enhance the pharmacokinetic behavior of incorporated drugs through several mechanisms: improving membrane permeability, increasing solubilization potential, facilitating intestinal absorption, modulating cytochrome P450 enzymatic activity, stimulating chylomicron formation, and enhancing lymphatic drug transport(5). From a pharmaceutical standpoint, NLCs exhibit favorable characteristics including high drug entrapment efficiency, controlled and sustained drug release, long-term physicochemical stability, and excellent scalability for industrial production(6).Additionally, they offer high biocompatibility and biodegradability, supported by comprehensive toxicological evaluations.While NLCs were initially optimized for parenteral administration, they have since been adapted for various delivery routes such as oral, dermal, transdermal, ocular, nasal, pulmonary, and rectal applications, broadening their therapeutic applicability across multiple domains . The **fig 1** illustrates the diverse therapeutic applications of Nanostructured Lipid Carriers (NLCs)(7). It highlights that NLCs can be utilized in treating various conditions, including microbial infections, skin disorders, oxidative stress, inflammation (via NSAIDs), wound healing, diabetes and hypertension, cancer, and central nervous system (CNS) disorders(8). This broad utility reflects the potential of NLCs in enhancing drug delivery across multiple therapeutic areas.

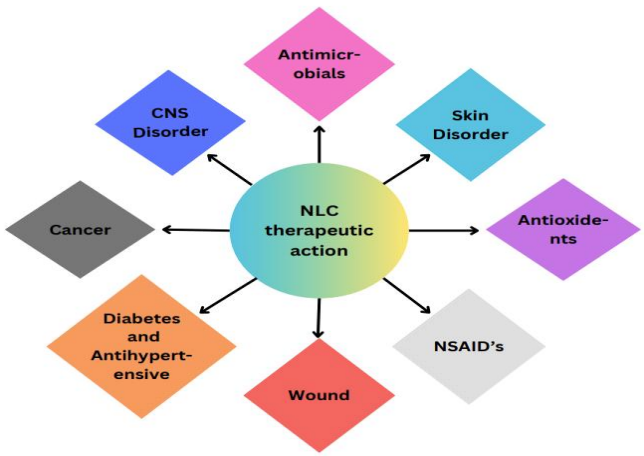

Fig 1: Therapeutic Action of NLC

Advantages of Nanostructured Lipid Carriers (NLCs)

Nanostructured Lipid Carriers (NLCs) have emerged as a superior alternative to traditional lipid-based delivery systems, offering several notable advantages:

1. Enhanced Drug Loading Capacity: The unique matrix of NLCs, comprising both solid and liquid lipids, creates structural imperfections that accommodate a higher amount of active pharmaceutical ingredients (APIs), particularly hydrophobic drugs with poor water solubility. (9)

2. Controlled and Targeted Drug Release: NLCs enable modulation of drug release kinetics, facilitating sustained and site-specific delivery, which enhances therapeutic efficacy and reduces side effects.

3. Improved Storage Stability: The inclusion of liquid lipids within the solid matrix minimizes drug expulsion during storage, thereby enhancing the formulation's stability over time. (10)

4. Versatile Drug Encapsulation: The hybrid lipid system of NLCs allows for the incorporation of both hydrophilic and lipophilic drugs, broadening their applicability across various therapeutic agents.
5. Biocompatibility and Biodegradability: Utilizing physiological lipids in NLC formulations ensures minimal systemic toxicity and promotes safe metabolism within the body.
6. Cost-Effective Production and Scalability: NLCs offer a more economical manufacturing process compared to polymeric carriers and can be efficiently scaled up using conventional equipment.(11)
7. Enhanced Physical Stability: The nanostructured lipid matrix resists phase separation and aggregation, maintaining particle integrity and ensuring consistent performance.
8. Ease of Preparation and Upscaling: Techniques such as high-pressure homogenization and ultrasonication allow for reproducible and scalable NLC production. (12)
9. Dermatological Advantages: NLCs improve skin hydration and elasticity through their occlusive effects, making them particularly beneficial in topical formulation.
10. Efficient Skin Penetration: The nano-size range (~50–200 nm) facilitates close interaction with the stratum corneum, enhancing transdermal and dermal drug delivery.
11. Protection of Encapsulated Drugs: The lipid matrix provides a protective environment that stabilizes labile drug molecules against hydrolytic and oxidative degradation.(13)

Disadvantages of Nanostructured Lipid Carriers (NLCs)
Despite their numerous advantages, NLCs also present certain challenges that need to be addressed:
1. Potential Cytotoxicity: The safety profile of NLCs can be influenced by the type and concentration of lipids and surfactants used, which may affect cytotoxicity.(14)
2. Surfactant-Induced Irritation: Prolonged exposure to certain surfactants in NLC formulations may lead to local irritation or hypersensitivity reactions, particularly with chronic use or topical applications. (15)
3. Limited Applicability for Macromolecules: Encapsulation and delivery of large biomolecules such as proteins, peptides, and nucleic acids remain challenging due to stability and delivery issues.
4. Insufficient Long-Term Clinical Data: There is a lack of comprehensive long-term preclinical and clinical studies evaluating the safety, efficacy, and therapeutic potential of NLC-based formulations, which hinders their widespread clinical adoption.(16)
Structures of NLC:
NLC has been classified into three different classes based on the nano-structure, composition and ratios of solid and liquid lipids- **(Fig.2)** (17)
1) Type I (The imperfect type)
2) Type II (The formless /amorphous type)
3) Type III (The multiple type) **(Table 1)**

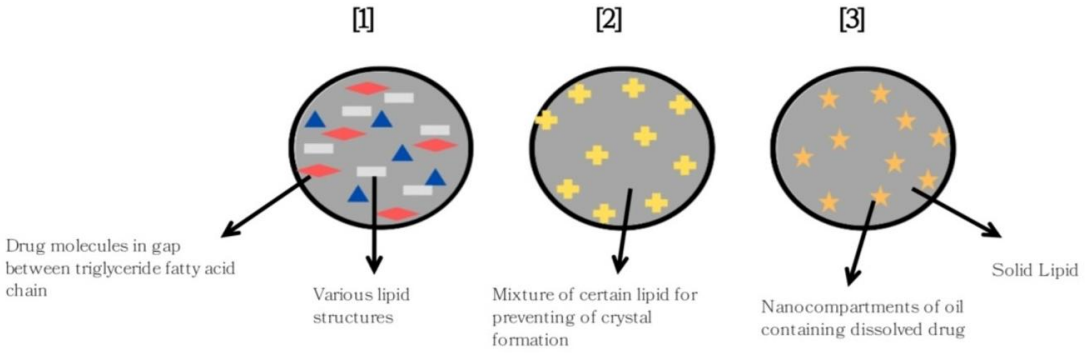

Fig 2 : Structure of NLC Class I(Imperfect Type), Class II (Formles type), Class III (Multiple type)

Type	Structure	Features	Drug loading	Stability
I– Imperfect	Defective crystal/ An irregularly arranged solid matrix	High entrapment	High (lipophilic drugs)	Moderate
II – Amorphous	Non-crystalline/ Construction appears less solid Amorphous matrix	No recrystallization	Uniform dispersion	High
III – Multiple	Oil compartments in solid lipid/ Various lipids/ oil in fat in water	Dual drug accommodation	Very high	Good

Table 1: Types of NLCs (18,19)

COMPOSITION OF NLCs:

The formulation of nanostructured lipid carriers (NLCs) involves the incorporation of various functional excipients, each contributing to the overall stability, drug loading capacity, and release behavior of the system. These components include solid lipids, liquid lipids, and surfactants, selected based on their physicochemical compatibility and ability to form stable nanoscale dispersions. The **table 2** summarizes commonly used ingredients along with representative examples employed in NLC formulations.

Ingredients	Materials
Solid lipid	Tristearin, stearic acid, cetyl palmitate, cholesterol, PrecirolATO 5. Compritol 888 ATO. Dynasan 8116, Dynasan B 118, Softisang 154, Cutina CP, Imwitor 900 P. Geleol, Gelot® 64, Emulcire 61, Glycerol trilaurate, Glyceryl dilaurate, Geleol (20-22)
Liquid lipid	Medium chain triglycerides, paraffin oil, 2-octyl dodecanol, oleic acid, squalene, isopropyl myristate, vitamin E, Miglyol® 812, Transcutol® HP, Labrafil M 1944CS, LipofileWL2609BS, Labrafac CC, Lauroglycol® FCC,Capryol® 90,Capmul MCM, Captex® 500 P, Olive oil (23,24)
Surfactant	Pluronic® F- 68 (Poloxomer 188), Pluronic® F-127, (Poloxomer 407), Sodium taurocholate Sodium dodecylsulfate, Tyloxapol, Cremophor EL, Cremophor RH40, Span 40, Polyvinyl alcohol, lecithin , Soy lecithin (S 75), Polysorbate 80 (Tween 80), Polysorbate 60 (Tween 60), Polysorbate 20 (Tween 20), DSPE-PEG (Distearoylphosphatidyl-ethanolamine PEG) (25,26)

Table 2 : Composition of NLCs

Method of Preparation of NLC

Nanostructured lipid carriers (NLCs) can be formulated using various techniques **(fig 3)** broadly classified into high-energy, low-energy, and organic solvent-based methods. Each approach differs in terms of equipment, energy input, and process conditions, which influence the particle size, stability, and drug entrapment efficiency. The choice of method is primarily guided by the

physicochemical properties of the drug and lipids used, as well as the intended route of administration.

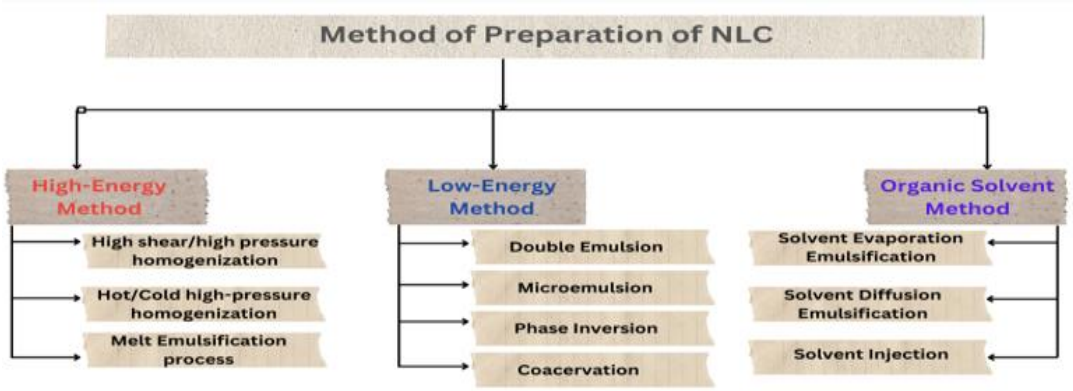

Fig 3 : Method of Preparation of NLC

High Shear/High-Pressure Homogenization Technique

In this method, both solid and liquid lipids are initially melted together at a temperature approximately 5–10 °C above the melting point of the solid lipid. The active pharmaceutical ingredient (API) is either solubilized or dispersed within this lipid melt.(27) Subsequently, an aqueous surfactant solution, preheated to the same temperature, is incorporated into the lipid phase to form a coarse pre-emulsion. This pre-emulsion is then subjected to high shear mixing or high-pressure homogenization to reduce the droplet size. **Fig 4** Upon rapid cooling, the hot oil-in-water nanoemulsion transitions into a nanostructured lipid carrier (NLC) dispersion with uniform particle distribution and nanoscale size.(28) This process may be further refined using ultrasonication to ensure enhanced homogeneity and stability of the final formulation.

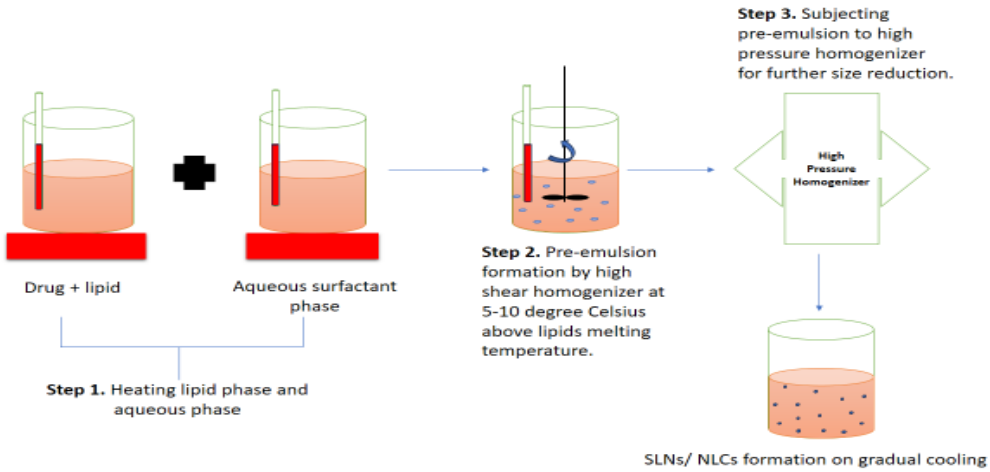

Fig 4. High pressure homogenization method

Hot High-Pressure Homogenization (HPH)

Hot high-pressure homogenization (HPH) is a widely utilized method for the large-scale production of nanostructured lipid carriers (NLCs). In this technique, intense mechanical forces generated by high pressure induce substantial shear stress, causing the breakdown of lipid particles into submicron or nanometer-sized dimensions(29). The process typically employs lipid concentrations in the range of 5% to 10% (w/w). A notable advantage of HPH is its scalability, as no significant technical challenges have been reported during transition from laboratory to industrial scale. **Fig 5** Depending on the formulation requirements, homogenization can be performed at elevated

temperatures—generally above the melting point of the lipid—or at lower temperatures under specific processing conditions(30).

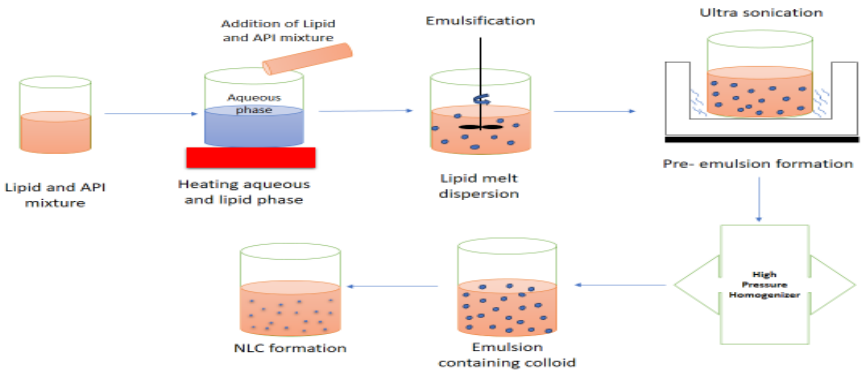

Fig 5. Hot HPH Method

Cold high-pressure homogenization:

The cold high-pressure homogenization (cold HPH) technique parallels the hot HPH method in initially dissolving the drug within molten lipids. However, following this, the drug-lipid mixture is rapidly cooled and solidified using cryogenic agents such as liquid nitrogen or dry ice.(31) The resulting solidified mass is then ground into microparticles via ball milling or mortar and pestle. These microparticles are subsequently dispersed in a chilled aqueous surfactant solution and homogenized at temperatures below ambient conditions. **fig 6.** This cold HPH process is particularly advantageous for formulating hydrophilic or thermosensitive drugs, as it minimizes thermal degradation and reduces drug partitioning into the aqueous phase during preparation.(32)

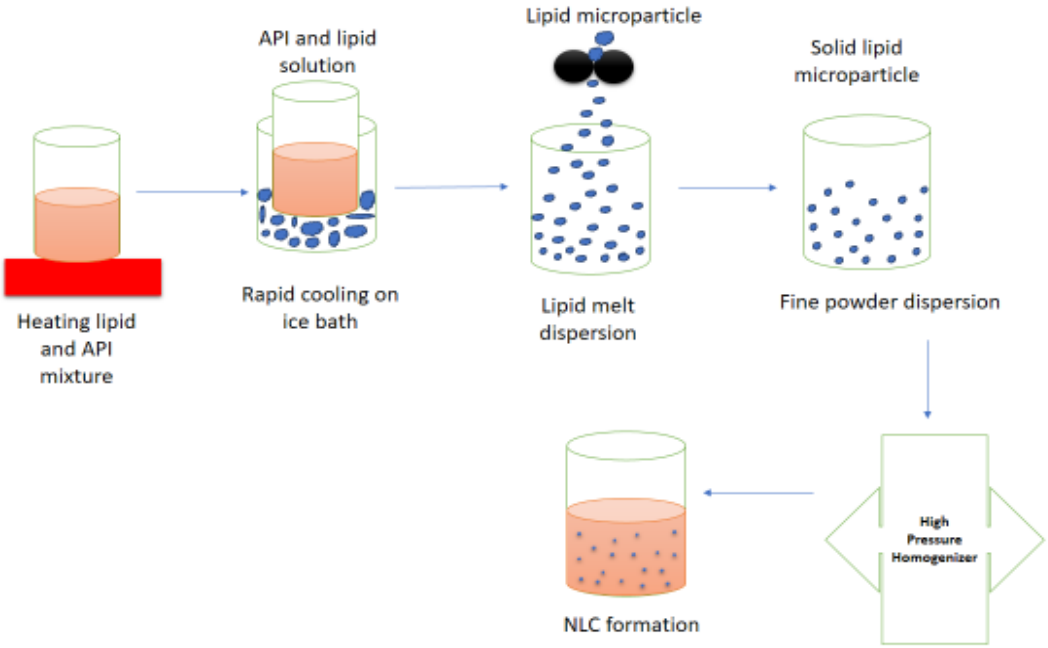

Fig 6. Cold HPH

Melt Emulsification Homogenization Technique :

in the melt emulsification homogenization technique, the solid lipid, liquid lipid, and drug are first combined and dispersed into an aqueous surfactant solution using probe sonication. (33)The resulting emulsion is then cooled to a low temperature, facilitating the formation of solid nanostructured lipid carriers (NLCs). **Fig 7** A key benefit of this method is its ability to minimize thermal exposure, thereby protecting heat-sensitive compounds during formulation.(34)

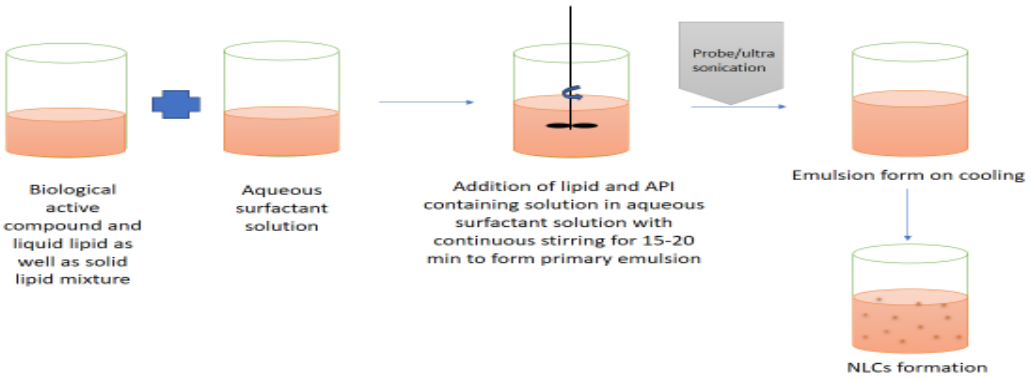

Fig 7. Melt Emulsification Method

Double Emulsion.

In the double emulsion technique, hydrophilic bioactive agents are first dispersed within a lipid phase comprising molten lipids, lipophilic drugs, and hydrophobic surfactants, forming a primary water-in-oil (W/O) emulsion.(35) This primary emulsion is subsequently re-emulsified into an external aqueous phase containing hydrophilic surfactants, resulting in a water-in-oil-in-water (W/O/W) double emulsion. **fig 8** Both emulsification steps are facilitated by sonication to ensure effective homogenization.(36)

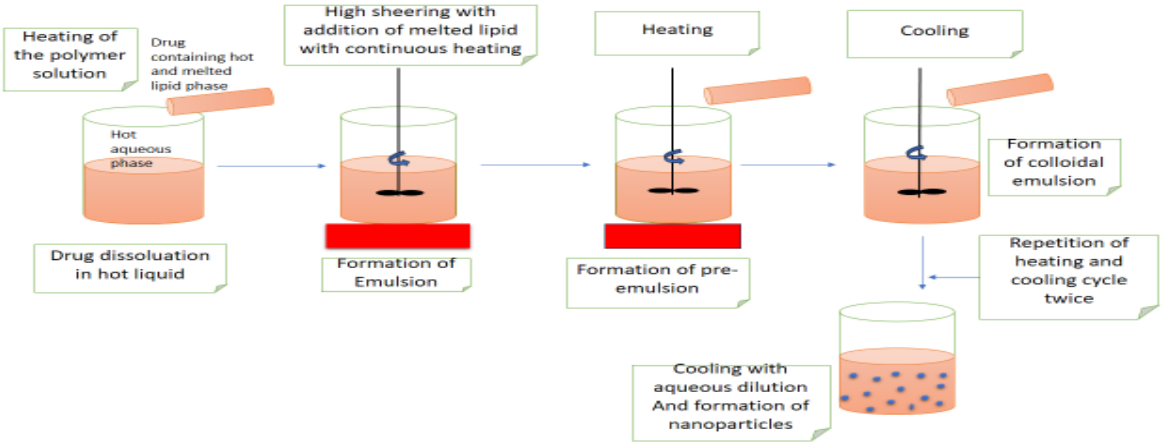

Fig 8. Double Emulsion Method

Microemulsion method

The drug is first incorporated into molten lipids. Simultaneously, water, surfactants, and cosurfactants are heated to match the temperature of the lipid phase. These components are then combined in precise proportions to form a transparent and thermodynamically stable microemulsion. This microemulsion is utilized to control the particle size effectively (37).Subsequently, the heated microemulsion is gently dispersed into a cold aqueous medium at a dilution ratio ranging from 1:25 to 1:50. The rapid addition of oil droplets into the cold aqueous phase induces immediate recrystallization, leading to the formation of nanoparticles.(38) **fig 9**

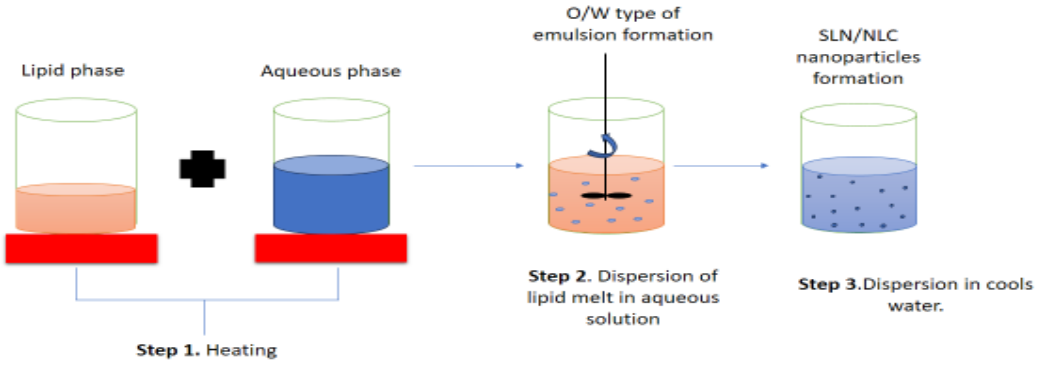

Fig 9. Microemulsion Method

Phase-Inversion Temperature Method

This method is distinguished by inducing a phase inversion from an oil-in-water (O/W) to a water-in-oil (W/O) emulsion, offering a unique and cost-effective solvent-free technique for lipid nanoparticle (LNP) production. Initially, the proportions of lipid, surfactant, and water are optimized, followed by gradual heating from room temperature up to 85°C, increasing in increments of 4°C. **fig 10** .The system undergoes three heating and cooling cycles to reach the phase inversion zone. In the subsequent step, rapid addition of cold water at 0°C imposes an irreversible perturbation, triggering the formation of stable nanocapsules.(39)

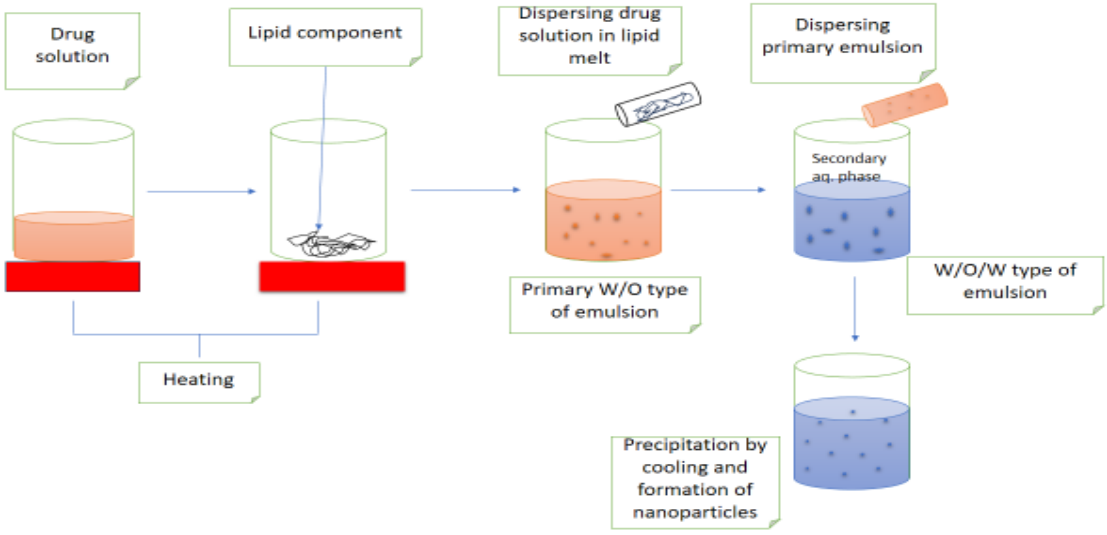

Fig 10. Phase Inversion Method

Coacervation Method

This method converts thermosensitive lipids into nanostructured lipid carriers (NLCs) without using harmful solvents. By adding an amphiphilic emulsifier to the lipid mixture in an acidic coacervation solution, a phase separation occurs, forming a coacervate that encapsulates and stabilizes the lipids.(40) **fig 11.** The acidic environment helps control emulsifier and lipid interactions, ensuring stable NLCs with preserved lipid integrity and suitable particle size.(41)

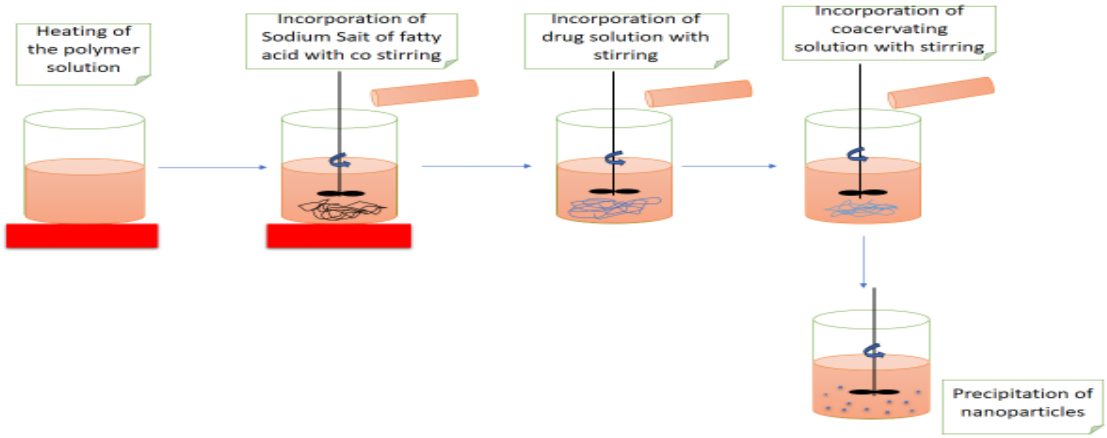

Fig 11. Coacervation Method

Solvent-emulsification evaporation technique

In the solvent-emulsification evaporation technique, solid and liquid lipids with the drug are dissolved in a water-immiscible organic solvent and emulsified into an aqueous surfactant solution to form an oil-in-water emulsion. The solvent is then removed under reduced pressure at low temperature, causing lipid precipitation and nanoparticle formation. This method minimizes heat exposure but requires organic solvents. Particle size typically ranges from 30 to 100 nm, depending on the lipid and surfactant used.(42) **fig 12**

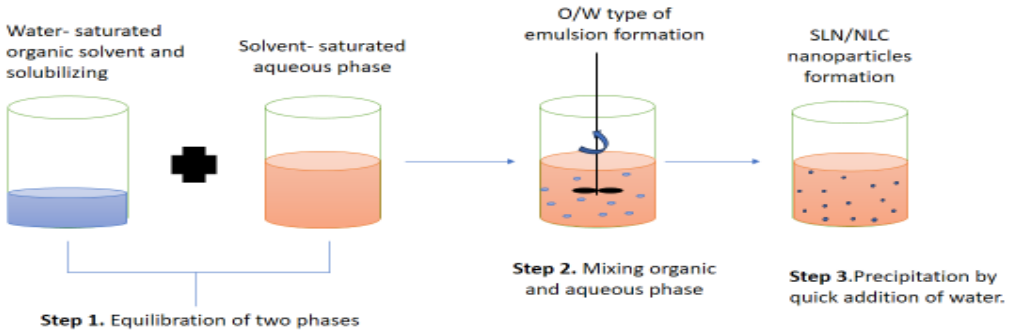

Fig 12. Solvent Evaporation Emulsification Method

Solvent Emulsification and Diffusion

This method exploits the water miscibility of organic solvents such as butyl lactate or benzyl alcohol used in the lipid phase. The drug and lipids are first dissolved in a water-miscible solvent to form a primary oil-in-water (O/W) emulsion. This emulsion is then introduced into an aqueous medium, where the solvent diffuses from the dispersed droplets into the surrounding water. As the solvent diffuses out, the lipophilic components precipitate and solidify, resulting in nanoparticle formation.(43)

Solvent Injection

In this technique, lipids are dissolved in water-miscible organic solvents like ethanol, acetone, or isopropanol and subsequently injected into an aqueous phase under continuous stirring. This rapid mixing leads to lipid precipitation and nanoparticle formation. (44)The dispersion is then filtered to remove any unincorporated lipids. The presence of an emulsifier in the aqueous phase promotes the formation of stabilized lipid droplets at the injection site, maintaining particle integrity until complete solvent diffusion occurs.(45) **fig 13**

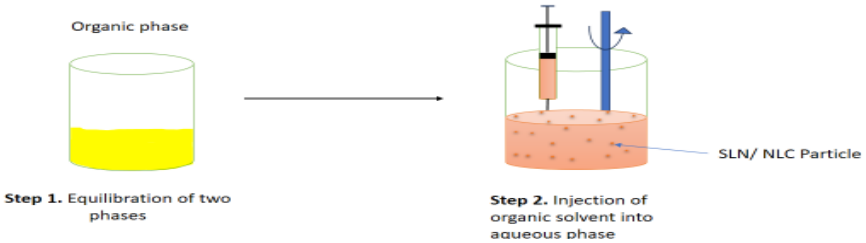

Fig 13. Solvent Injection Methode

Structure of skin barrier:

The skin barrier, primarily constituted by the stratum corneum, acts as the principal obstacle to topical drug delivery, owing to its tightly packed lipid matrix and regulated microenvironment factors such as pH, moisture, and enzymatic activity (46). Nanostructured Lipid Carriers (NLCs) have emerged as promising lipid-based nanocarriers designed to overcome these intrinsic barrier limitations by enhancing drug penetration and controlled release profiles (47). The unique composition of NLCs, involving a blend of solid and liquid lipids, facilitates improved skin hydration and disrupts the stratum corneum lipid organization, thus modulating barrier properties without compromising skin integrity. Moreover, NLC formulations enhance drug solubility and stability while allowing for targeted and sustained delivery, effectively addressing challenges associated with molecular size and lipophilicity that typically hinder percutaneous absorption (48). Penetration enhancers incorporated within NLCs further augment drug permeation by transiently altering skin lipid fluidity and protein conformation. Collectively, these attributes underscore the potential of NLCs to optimize topical therapy by harmonizing with the skin's complex barrier mechanisms and enhancing therapeutic efficacy (49).

Topical Application of Nanostructured Lipid Carrier

Nanostructured lipid carriers (NLCs) offer an effective topical drug delivery system by enhancing skin penetration, drug retention, and therapeutic efficacy. Their biocompatible lipid matrix supports sustained release while reducing systemic absorption and irritation. Various drugs have been incorporated into NLCs for dermatological, antifungal, anti-inflammatory, and cosmetic applications, as summarized in the **table 3**

Sr. No	Title	Marketed product	Drug	Method of Preparation	Purpose	Observation	Conclusion
1.	**Topical Therapy Drug for NLCs**	**Nolvadex**	**Tamoxifen citrate (50)**	Emulsification cum sodilification -High speed homogenite	-Psoriasis -Restricted penetration through the skin and greater drug retention in the epidermal and dermal layers for a lengthy period of time - enhance	-Viscous gel having pH similar to skin and smooth texture	-Ensured longer stay due to semisolid consistency over the skin -Due to the presence of hydrophic gelling polymer which increases skin moisture -Improve

					the hydration of the skin and lipid content.		drug retention
		Altreno	**Tretinoin (Derivative of vit A) (51)**	Hot melt microemulsion and hot melt probe sonication method	-Anti-aging and anti-acne potential For reducing skin irritation potential, increasing the drug loading capacity and prolonging the duration of action	-Size- 1 to 100 nm -pH- 7.0±0.2 -Stability- refrigeration temperature(4 $\pm 2^0$c), room temperature(27-2^0c) -Entrapment efficiency- 97-98%	Tretinoin loaded NLC have been able to reduce the irritation of the skin
		Griseofulvin V, Griseocream	**Griseofulvin (52)**	Sonication	Dermatophytosis Griseofulvin loaded nanogel increased the oxidant efficacy of the drug and therefore enhancement of the drug in nanogel formation	-Particle size- 209nm -Zetapotential = -44.12 mV -Entrapment level = 85.24 % -Drug release = 92.12 % -Stability = RT-25±2^0C Refrigarator Temp- 4±2^0C	It revealed the prospective of the nanogel in the treatment of superficial infections like ringworm anstenia pedis consequently, it could be an effective alternative for currently existing product.
		B Airtal Aceclo Acebel-p Zerodol	**Aceclofenac (53)**	-Melt emulsification and low temp solidification - Ultrasonication method -High speed	-Analgesic - Antipyretic -Anti-inflammatory treatment for various kind of	-Partical size = 1 µm -Volume of distribution = 90 % -Zeta potential = -9.3 to – 12.8 mV -Entrapment	It is also found that the release rate, permeation rate, and pharmacodynamic activity can

				homogenizer method	pain -Osteoarthritis, Rheumatoid arthritis	level = 69.92% to 82.09% -pH =6.78 -Solubility = 58 µg/mL -Dissolutiom rate = 90 min	be modulated upon changing the ratio of solid lipid to liquid lipid. It can be concluded that the optimized NLC gels exhibit faster onset and prolonged action as compared to the marketed product. Further, *in vivo* pharmacokinetic studies are necessary to assess the improvement of therapeutic efficacy of the NLC gel compared to the marketed product.
		Curcumin and EGF	**Curcuma Longa.(54)**	W/O/W double emulsion method	-Wound,burns, and diabetic ulcer -Hemostasis, Anti-inflammation -Tissue remodeling	-Spherical partical size – 331.8 nm -Encapsulation efficiency – 81.8- 99.4% -Solubility - poor	EGF-cur NLCs increases the activivty of antioxidant enzyme -It improve the migration &proliferation of fibroblast and keratinocytes
		Ranolazines	**Ranexa(55)**	High pressure	-Angina pectoris	-Entrapment effectiveness=	-The final product

				homonizatio n method	and Hypertensi on. -Anti- anginal agent, Myocardial infraction Cardiac arrhythmia s	88.39± 3.1% -Particle size= 118.4±5.94 nm. - Polydispersity index = 0.118± 0.028. -Zeta potential= - 41.91± 0.38	consistency, drug concentratio n,pH& rheological characterizat ion were enhanced by incorporated the nanolipid formulation into a gel matrix. Invivo&Exvi vo trial most efficient lipid carrier which allow them to permeate the skin.
		Meloxica m	**Mobic Vivlodex (56)**	Microencaps ulation method	Used as controlled release drug NSAID Joint disorder, rheumatoid arthritis.	Entrapment efficiency= 85.61± 1.35 %. Particle size= 195- 210 nm. Zeta potential= - 25mV - 27 mV.	Meloxicam NLC gel revealed biocompatibi lity Good skin tolerance & significant anti- inflammator y activity without any toxicity.
		B-Sitostero l	**Stigmastero l Campestero l Brassicaster ol** (57)	Encapsulatio n method	Used for treatment of alopacia	-Particle size = 173.67 ±52 nm. Polydispersity index = 0.3 -High zeta potential value	Ex vivo skin penetration study show higher permeation amount of β sitosterol.
		Miconaz ole nitrate	**Monistat (58,59)**	hot high pressure homogenizati on technique	well established as anti- mycotics for the treatment of topical fungal infections.	particle size lower than 300 nm . viscosity =0.8872 cP Polydispersity index = 0.350±0.003 zeta potential = -19.6±0.9	Using a modified HPH technique, MN-loaded NLC was successfully integrated into a hydrogel for

						entrapment efficiency= 80% to 100%	topical treatment. The developed methods offer a promising alternative for topical drugs delivery.
		Econazole nitrate	**Ecoza, Spectazole** (60.61)	hot homogenization technique	skin infections by dermatophytes	Partical size= 134.83 nm to 182.8 nm Polydispersity index= 0.27-0.39. Zeta Potential= -22.16 to -47.4 mV entrapment efficiency= 74.63±0.04% drug released= 8 hrs	This hybrid method has the potential to significantly improve antifungal efficacy and patient compliance in the treatment of dermatophytes.
		Ketoconazole	**1. Ketoderm (62)**	melt-dispersion ultra-sonication method	Used in the treatment of superficial and systemic fungal infections. To minimize the adverse side effects and to prolong release.	average particle size= 125.8 ± 1.8 to 295.0 ± 3.8 nm zeta potential= -13.2 ± 1.1 to -30.9 ± 2.2 mV percentage entrapment= 69.47 ± 2.8 to 95.49 ± 4.5	The created nanostructured lipid-carrier gel formulation provides a promising carrier for topical ketoconazole delivery, as it has regulated drug release and skin targeting capability.

Table 3 : Advantages and Application of Nanostructured Lipid Carrier

Characterization of Nanostructured Lipid Carriers (NLCs)

Nanostructured Lipid Carriers (NLCs) are advanced drug delivery systems that require thorough characterization to ensure their efficacy and stability.Each of these parameters is crucial for determining the performance of NLCs in therapeutic applications

Particle Size and Polydispersity Index (PDI)

Particle size is a critical factor influencing drug release rate, skin penetration, and overall bioavailability. It is typically measured using Dynamic Light Scattering (DLS). Optimal particle sizes for NLCs usually fall within 50–200 nm. Polydispersity Index (PDI) assesses the size distribution homogeneity. A value between 0.1 and 0.3 indicates a narrow and uniform size distribution.(63)

Zeta Potential

Zeta potential reflects the surface charge of nanoparticles and is indicative of their colloidal stability. A zeta potential of ±30 mV or higher generally provides sufficient repulsion to prevent aggregation, thereby enhancing shelf-life and dispersion stability (63)

Entrapment Efficiency (EE%)

Entrapment Efficiency (EE%) evaluates the proportion of drug successfully encapsulated inside the lipid matrix: (64)

EE%= Total Drug − Free Drug / Total Drug × 100

Drug Loading (DL%)

Measures the drug content relative to the total weight of NLCs. These parameters are essential for optimizing dosage and release profile (64)

DL%= Total Drug − Free Drug Total Weight of Nanoparticles × 100

Morphological Analysis

Morphological evaluation using Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) helps to assess particle shape, surface structure, and aggregation. Spherical and smooth-surfaced particles often indicate a well-formed and stable NLC system (65)

Crystallinity and Polymorphism

The degree of crystallinity is studied using Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD). Amorphous or less crystalline matrices can accommodate more drug, improving loading efficiency and release uniformity (65)

In Vitro Drug Release

This test determines the kinetics and mechanism of drug release from NLCs using techniques such as Franz diffusion cells or dialysis membrane methods. It provides predictive insight into the drug's performance in vivo (66)

Stability Studies

Stability assessments monitor particle size, zeta potential, drug content, and physical appearance over time under various storage conditions. These studies help establish shelf life and ensure product safety and efficacy (66)

Futures Perspective of Antifungal NLC

The future of antifungal therapy using nanostructured lipid carriers (NLCs) holds significant promise due to their superior drug loading capacity, controlled release behavior, and ability to enhance skin penetration and bioavailability of poorly soluble antifungal agents(67). Emerging innovations such as targeted delivery, surface-modified NLCs, and stimuli-responsive systems are expected to enhance therapeutic outcomes while reducing systemic toxicity and drug resistance(68). Moreover, integrating NLCs with advanced delivery platforms like microneedles and hydrogels could revolutionize the management of both superficial and deep fungal infections. To enable clinical translation, further research into excipient safety and regulatory standardization remains essential(69).

List of Patents on Nanostructured lipid carrier

No.	Patent No.	Applicant of patent	Title of Patent	Description
1	RO135202	Ac helcors.r.l. (70)	Process for dual encapsulation of two categories of bioactive plant based principles in the same nanostructure distribution system	The invention comprises a dual nanocarrier. The NLC formulation contains licorice extract & wild yam extract which provide sustained release and enhance antioxidant & anti-inflammatory effect
2	AU2021104270	Fatma, Bushra Kumar, Vikram Kushwaha, Swatantra K S Mantry, Shubhrajit Mohanto, Sourav Srivastava, Dipti Tiwari, Pallavi (71)	Desvenlafaxine succinate loaded Nanostructured lipid carrier (NLC) for brain targeting via nasal route	The NLC preparation improved the bioavailability of the lipophilic drugs by crossing the Blood – Brain Barrier through the nasal route and producing an antidepressant effect
3	US15163724	Hamidreza Kelidari Majid Saeedi (72)	Topical nano drug formulation	The prepared NLC gel contains spironolactone as a biomolecule for acne vulgaris disorder. The formulation shows improved skin penetration and drug release
4	AU2021104317	Nnamani, Petra Obioma (73)	An Artemether-Loaded Nanostructured Lipid Carrier (NLC) Nanogel Composition and a Method for Formulation of the Artemether-Loaded (NLC) Nanogel	The research involves the preparation of lyophilized NLC formulation and covert into a gel for the treatment of malaria.
5	AU2018285694	Infectious Disease Research Institute(74)	Nanostructured lipid carriers and stable emulsions and uses thereof	To prepare NLC containing lipid phase along with other oil core which delivers the active ingredient to cell for generating of immune response like the vaccine
6	WO2016065444	UniversidadeEstadua l De Campinas -Unicamp [BR]/[BR] (75)	Method for producing nanostructured	The Present invention related to producing NLC with triblock

			lipid carriers on triblock copolymers, nanostructured lipid carriers thereby produced and uses thereof.	copolymer (one liquid lipid & two solid lipids) using hot homogenization as the method. This cosmetic preparation is used for moisture retention in the hair fiber.
7	US20080020058A1	Sirna Therapeutics, Inc., San Francisco, CA (US) (76)	Compositions and methods for delivering physiologically active chemicals utilizing lipid nanoparticles	The invention involves new cationic lipids and nanoparticles that deliver active molecules like antibodies and nucleic acids to cells, useful for treating diseases by modulating gene expression.
8	US20100247619A1	Consiglio Nazionale Delle Ricerche, Roma (IT): Universita Degli Studi Di Catania, Catania (IT): Universita Degli Studi Di Palermo, Palermo (IT) (77)	Pharmaceutical formulations containing solid particles and nanostructured lipid carriers containing riluzole	This invention relates to nanoparticles consisting of riluzole trapped in lipids, and their use to prepare medicinal products for the treatment of Amyotrophic Lateral Sclerosis and Mul tiple Sclerosis.
9	US20220054416A1	Infectious Disease Research Institute (78)	Nanostructured lipid carriers and stable emulsions and uses thereof	The invention provides nanostructured lipid carrier (NLC) compositions, including their preparation and use. These NLCs, made of a mix of liquid and solid lipids, cationic lipids, sorbitan esters, and hydrophilic surfactants, can deliver bioactive agents to cells to generate immune responses for vaccines, therapies, or diagnostics.
10	WO2023023492	Unchained Labs (79)	Methods, compositions, and devices for making solid lipid nanoparticles and nanostructured lipid carriers	The invention includes fluidic and microfluidic devices, and assemblies, for making and monitoring particles or protein precipitates. These devices feature

				channels connecting a reaction well to inlet and outlet ports, with a constriction channel to retain fluids and promote mixing. They can be used individually or interconnected for continuous processes.

Table 5: List of Patents on Nanostructured lipid carriers.

Conclusion

Nanostructured lipid carriers (NLCs) signify a paradigm shift in the domain of lipid-based nanotherapeutics, offering superior drug-loading efficiency, enhanced physicochemical stability, finely tunable release kinetics, and exceptional biocompatibility when compared to conventional solid lipid nanoparticles (SLNs). Their dual capacity to encapsulate both hydrophilic and lipophilic bioactives, alongside their proficiency in traversing biological barriers, renders them exceptionally adaptable for multiple routes of administration—including topical, oral, and parenteral delivery. The strategic incorporation of functional excipients and surface-engineered ligands has further augmented their potential for site-specific targeting and improved pharmacodynamic profiles. Advancing the clinical translation of NLCs necessitates a multidisciplinary approach emphasizing formulation refinement, scalable manufacturing methodologies, rigorous toxicological evaluation, and regulatory harmonization. In alignment with the evolving trajectory of precision medicine, NLCs are poised to emerge as a pivotal platform technology in the next era of intelligent and patient-centric drug delivery systems

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this work.

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