Ibuprofen-Loaded Nanogels: Advancing Topical Therapy Through Nanoengineered Drug Delivery Systems

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Abstract **- Ibuprofen, a commonly used non-steroidal anti-inflammatory drug (NSAID), exhibits limitations such as poor aqueous solubility (BCS Class II), short half-life, and gastrointestinal side effects, which restrict its therapeutic efficiency. To overcome these challenges, ibuprofen-loaded nanogels have been developed as an advanced drug delivery system for enhanced localized and transdermal delivery. These nanogels are prepared using high-energy methods (such as high-pressure homogenization, microfluidization, and ultrasonication) and low-energy techniques (including phase inversion and self-nanoemulsification), forming a stable three-dimensional polymeric network with key excipients like Carbopol 934 and Tween 80. With particle sizes ranging from 20–200 nm, nanogels improve solubility, provide high drug encapsulation efficiency (>90%), and enable controlled drug release following Higuchi and Korsmeyer–Peppas kinetics. Overall, ibuprofen nanogels enhance dermal permeation, ensure sustained drug release, reduce dosing frequency, and minimize systemic side effects, making them a promising approach for the treatment of localized inflammatory conditions.**

Keywords: **Ibuprofen, Nanogel, Nanoemulsion, Transdermal Delivery, Carbopol 934, NSAIDs, Controlled Release.**

I. INTRODUCTION

1. Background and Significance of Ibuprofen in Therapy

Ibuprofen is one of the most widely prescribed non-steroidal anti-inflammatory drugs (NSAIDs), belonging to the class of propionic acid derivatives. It is extensively used for its analgesic, anti-inflammatory, and antipyretic properties. The pharmacological action of ibuprofen is primarily attributed to the inhibition of cyclooxygenase enzymes (COX-1 and COX-2), which are responsible for the conversion of arachidonic acid into prostaglandins—key mediators of inflammation, pain, and fever.

Due to its effectiveness and relatively fast onset of action, ibuprofen is commonly used in the management of conditions such as rheumatoid arthritis, osteoarthritis, dysmenorrhea, dental pain, musculoskeletal injuries, and postoperative inflammation. It is available in multiple dosage forms including tablets, capsules, suspensions, and topical gels.

However, despite its widespread use, ibuprofen therapy is associated with several pharmacokinetic and pharmacodynamic limitations. One of the most significant drawbacks is gastrointestinal toxicity, which arises due to inhibition of prostaglandin synthesis that normally protects the gastric mucosa [1] [2]. Long-term use can lead to serious complications such as gastric ulceration, bleeding, and perforation. Additionally, ibuprofen undergoes extensive hepatic first-pass metabolism, resulting in reduced systemic bioavailability.

Another limitation is its short biological half-life (approximately 2 hours), which necessitates frequent dosing and may lead to poor patient compliance. Furthermore, systemic administration can result in adverse effects such as renal dysfunction, cardiovascular risks, and hypersensitivity reactions. These challenges highlight the urgent need for innovative drug delivery systems that can enhance therapeutic efficacy while minimizing adverse effects.

2. Need for Novel Drug Delivery Systems

The limitations associated with conventional drug delivery systems have driven significant research toward the development of novel drug delivery approaches. An ideal drug delivery system should:

Deliver the drug at a controlled and sustained rate

Maintain therapeutic drug concentration for an extended period

Reduce dosing frequency

Improve patient compliance

Minimize systemic side effects

Enable targeted or site-specific delivery

In this context, nanotechnology has emerged as a transformative tool in pharmaceutical sciences. Nanocarriers such as nanoparticles, liposomes, dendrimers, nanoemulsions, and nanogels have

shown remarkable potential in addressing the limitations of conventional drug delivery systems .[2] [3] Among these, nanogels are particularly attractive due to their unique combination of nanoscale size and hydrogel properties, which allow them to function as efficient drug carriers.

3. Nanotechnology-Based Drug Delivery Systems

Nanotechnology involves the design and application of materials at the nanoscale (1–100 nm), where unique physicochemical properties can be exploited for biomedical applications. In drug delivery, nanotechnology enables the development of systems that can improve drug solubility, stability, bioavailability, and targeting efficiency.

Nanocarriers provide several advantages, including:

Increased surface area, enhancing drug loading

Improved interaction with biological membranes

Ability to cross biological barriers such as skin and mucosa

Controlled and stimuli-responsive drug release

These features make nanotechnology-based systems highly suitable for delivering poorly soluble drugs like ibuprofen.

4. Nanogels: Concept and Structural Features

Nanogels are defined as nanosized, three-dimensional crosslinked polymeric networks that can absorb and retain large amounts of water or biological fluids without dissolving [3,4]. They represent a unique hybrid system combining the advantages of hydrogels (swelling, biocompatibility) and nanoparticles (small size, high surface area).

4.1 Structural Architecture of Nanogels

The structure of nanogels consists of:

A polymeric backbone forming the network

Crosslinking points (physical or chemical)

Interconnected pores or mesh-like structure

This porous structure allows drug molecules to be encapsulated within the network and released in a controlled manner.

4.2 Physicochemical Properties

Nanogels exhibit several important properties:

Particle size (20–200 nm): Facilitates deep tissue and skin penetration

High swelling capacity: Enables efficient drug loading

Soft and deformable nature: Allows passage through biological barriers

Biocompatibility and biodegradability: Ensures safety

High surface area: Enhances interaction with target tissues

Stimuli responsiveness: Enables controlled drug release

These properties make nanogels particularly suitable for transdermal drug delivery, where penetration through the stratum corneum is a major challenge.

5. Classification of Nanogels

5.1 Based on Polymer Source

Natural polymers: Chitosan, alginate, dextran, gelatin

Synthetic polymers: PNIPAM, PEG, polyacrylic acid

Hybrid systems: Combination of natural and synthetic polymers

Natural polymers offer biocompatibility, whereas synthetic polymers provide mechanical strength and stability.

5.2 Based on Stimuli Responsiveness

Nanogels can be designed to respond to specific environmental triggers:

pH-sensitive nanogels: Release drug in acidic or basic environments

Thermosensitive nanogels: Respond to temperature changes

Enzyme-responsive nanogels: Degrade in presence of specific enzymes

Multi-responsive nanogels: Respond to multiple stimuli simultaneously

These systems are highly useful for targeted drug delivery in diseased tissues [4]

5.3 Based on Crosslinking

Physical crosslinking: Reversible, less stable

Chemical crosslinking: Covalent bonds, more stable and durable

6. Mechanism of Drug Delivery from Nanogels

The drug delivery process involves multiple physicochemical phenomena:

6.1 Drug Incorporation

Ibuprofen, being hydrophobic, is incorporated into the nanogel matrix through:

Hydrophobic interactions

Van der Waals forces

Polymer-drug compatibility

6.2 Swelling and Diffusion

Upon contact with aqueous media, nanogels absorb water and swell, increasing mesh size and allowing drug molecules to diffuse outward.

6.3 Controlled Release Mechanisms
Diffusion-controlled release
Swelling-controlled release
Erosion/degradation-controlled release
Mathematical models such as:
Higuchi model
Korsmeyer–Peppas model
are used to describe release kinetics [7]

6.4 Skin Penetration Mechanism
Nanogels enhance transdermal delivery by:
Hydrating the stratum corneum
Disrupting lipid bilayers
Increasing drug partition coefficient
Enhancing retention at the site of application

7. Ibuprofen Nanogels: Rationale and Advantages
Ibuprofen nanogels have been developed to overcome the limitations of conventional formulations. These systems offer:
Improved solubility of ibuprofen
Enhanced bioavailability
Sustained drug release
Reduced dosing frequency
Minimized gastrointestinal side effects
Localized drug delivery
Nanogels are particularly useful in treating localized inflammatory conditions, where topical delivery is preferred over systemic administration.
8. Recent Advances in Ibuprofen Nanogel Research
Recent studies have focused on:
Chitosan-based nanogels for enhanced bioadhesion
Thermosensitive nanogels for controlled release
Hybrid nanogels for improved stability
Nanoengineered gels with high encapsulation efficiency (>90%)
These advancements demonstrate the growing potential of nanogels in modern drug delivery systems .[1 6]

9. Overall Significance
Nanogels represent a next-generation drug delivery system that integrates nanotechnology with polymer science to enhance therapeutic outcomes. Their unique ability to provide controlled, targeted, and sustained drug delivery makes them highly suitable for ibuprofen and other NSAIDs.
With ongoing research and technological advancements, nanogels are expected to play a crucial role in future pharmaceutical formulations and clinical applications.

II. REVIEW OF LITERATURE

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Aim of the study

The overarching aim of the present investigation is to design, develop, and evaluate a translationally viable nanoengineered drug delivery platform for ibuprofen by synthesizing a polymer-based nanogel system (e.g., Carbomer or PLGA-based matrix). This study intends to systematically bridge the gap between material-level innovation and clinical performance by integrating nanotechnology with topical drug delivery strategies.

Specifically, the research focuses on exploiting nano-scale spatial confinement to enhance the physicochemical and biopharmaceutical properties of ibuprofen, a BCS Class II drug characterized by poor aqueous solubility and limited bioavailability. By incorporating ibuprofen into a three-dimensional crosslinked polymeric nanogel network, the study aims to achieve improved solubilization, enhanced thermodynamic stability, and controlled drug release behavior.

Furthermore, the developed nanogel system is expected to facilitate superior percutaneous absorption by reducing particle size to the nanometric range (20–200 nm), thereby increasing surface area and enabling efficient interaction with the stratum corneum. The incorporation of suitable surfactants and penetration enhancers is also intended to modulate the barrier properties of the skin, promoting deeper drug permeation and localized therapeutic action.

In addition, the study evaluates critical quality attributes such as particle size distribution, polydispersity index, zeta potential, encapsulation efficiency, rheological properties, and in vitro drug release kinetics, with a particular emphasis on diffusion-controlled release mechanisms (Higuchi and Korsmeyer–Peppas models).

Ultimately, this research seeks to demonstrate that nanoengineered ibuprofen nanogels can significantly outperform conventional dosage forms by offering enhanced bioavailability, sustained drug release, reduced dosing frequency, and minimized systemic side effects, thereby establishing a promising and clinically relevant approach for the effective management of localized inflammatory conditions.

III. OBJECTIVES OF THE STUDY

To design, formulate, and optimize a polymer-based ibuprofen nanogel system for enhanced transdermal drug delivery and improved therapeutic efficacy.

To select and characterize suitable polymers and excipients (e.g., Carbomer/PLGA, surfactants, penetration enhancers) for stable nanogel formulation.

To prepare ibuprofen-loaded nanogels using appropriate high-energy and/or low-energy techniques.

To reduce particle size to the nanometric range (20–200 nm) in order to enhance surface area and drug permeation.

To evaluate physicochemical properties of the nanogel, including:

Particle size and polydispersity index (PDI)

Zeta potential

pH, viscosity, and spreadability

To determine drug encapsulation efficiency and drug content uniformity of the formulation.

To study in vitro drug release behavior and fit the data into kinetic models such as Higuchi and Korsmeyer–Peppas.

To assess ex vivo/percutaneous drug permeation through suitable membrane or skin models.

To evaluate the stability of the nanogel formulation under different storage conditions.

To compare the performance of nanogel with conventional ibuprofen gel in terms of drug release and permeation.

To ensure safety and skin compatibility through irritation or patch testing.

Formulation Techniques of Nanoemulsion Drug Delivery Systems

The approaches used for the preparation of nanoemulsion-based drug delivery systems are varied and often overlap in their mechanisms. These techniques can be broadly categorized based on energy input, phase inversion behavior, and self-emulsification processes.

High-Energy Methods

High-pressure homogenization

Microfluidization

Ultrasonication

Low-Energy Methods

i) Phase inversion emulsification method

Transitional Phase Inversion (TPI):

Phase Inversion Temperature (PIT)

Phase Inversion Composition (PIC)

Catastrophic Phase Inversion (CPI):

Emulsion Inversion Point (EIP)

ii) Self-Nano emulsification method

1. High-Energy Methods

High-energy emulsification processes are primarily controlled by the energy density (E_v) applied to the system. The performance of these techniques is commonly evaluated using the Laplace pressure ($\Delta P = 2\gamma/r$), which represents the minimum mechanical stress required to disrupt droplets.[18] In high-energy approaches, specialized mechanical equipment generates strong disruptive forces that must exceed this pressure to achieve droplet breakup. As the droplet radius (r) decreases to the nanoscale, the total interfacial surface area increases markedly, thereby demanding substantially higher energy input for effective emulsification.

High-Pressure Homogenization (HPH)

HPH is a top-down approach where a coarse pre-emulsion is accelerated through a narrow homogenizing gap. High-pressure homogenization (HPH) is widely used at the industrial level to produce stable sub-micron dispersions.

Detailed mechanism: During homogenization, the pre-emulsion is subjected to elongational flow, intense turbulence, and cavitation. When the fluid passes through the narrow homogenization valve, its velocity rises sharply while the pressure drops. This sudden pressure decrease promotes the formation and subsequent collapse of vapor bubbles (cavitation). The resulting shockwaves, along with turbulent eddies, effectively break the droplets, typically reducing particle size to the 50–200 nm range and, under optimized conditions, to below 100 nm .[11]

Citation insight: Increasing the number of homogenization cycles generally decreases droplet size and narrows the polydispersity index (PDI). However, beyond

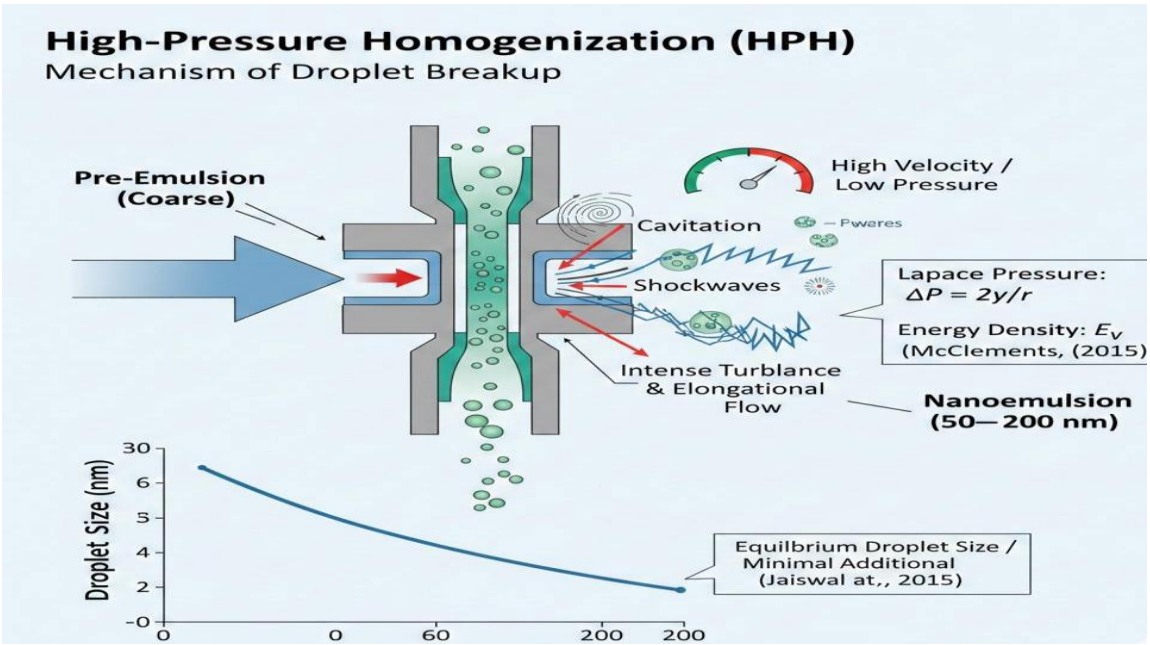


Fig.1.Mechanism of droplet breakup

a certain point, a plateau is reached where further energy input produces minimal additional size reduction [9]

Microfluidization

Microfluidization differs from HPH by using a fixed-geometry "interaction chamber."

Microfluidization is commonly differentiated from conventional high-pressure homogenization by the specialized design of its interaction chamber.

Mechanism: In this process, the emulsion is pressurized to very high levels (up to about 40,000 psi) and divided into two high-velocity streams that are directed through micro-channels (typically Y- or Z-type). These streams collide at a defined impingement zone, generating intense shear, turbulence, and particle-on-particle impact. The combined forces efficiently disrupt droplets and produce highly uniform nanoscale dispersions with very narrow polydispersity indices.[10]

Microfluidization is particularly advantageous for encapsulating lipophilic active compounds within nanogel systems. The well-controlled and consistent shear environment promotes uniform drug distribution throughout the polymer matrix, thereby enhancing formulation homogeneity and stability.[20]

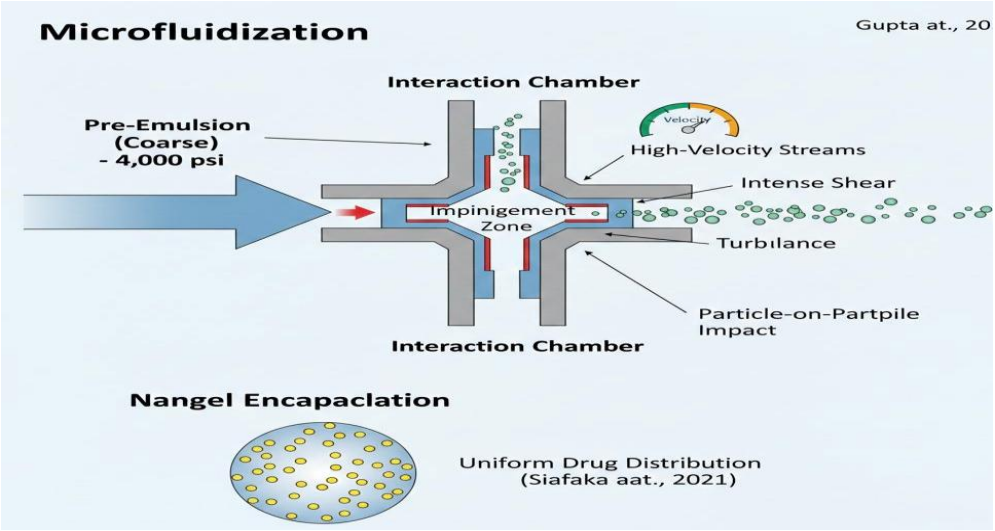


Fig.2.Microfluidization

Ultrasonication

Ultrasonication is one of the most widely used laboratory techniques for nanogel preparation, including formulations such as ketoprofen–PEA systems, mainly because of its simplicity and operational convenience.

Mechanism: The method is based on acoustic cavitation produced by high-frequency sound waves (>20 kHz). These waves generate alternating compression and rarefaction cycles within the liquid medium. During rarefaction, microscopic vapor bubbles form, and during compression, these bubbles collapse violently. The implosion of these microvoids produces localized “hot spots” with extremely high temperatures (≈5000 K) and pressures (≈1000 atm), creating intense shear forces that fracture drug crystals and emulsion droplets into nanoscale sizes.[19]

Critical factor: Process parameters such as probe position and pulse duration are crucial. Excessive or continuous sonication may lead to over-processing, where increased Brownian motion promotes droplet coalescence and reduces formulation stability [15]

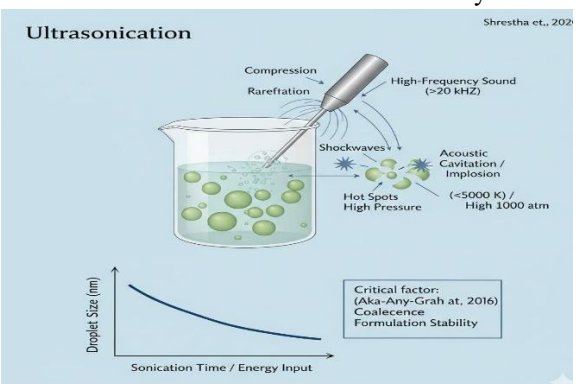


Fig.3.Ultrasonication

2. Low-Energy Methods

These methods utilize the chemical energy stored in the components. They are favored for being "green" and energy-efficient, as they rely on spontaneous emulsification during a phase transition.

i) Phase Inversion Emulsification (PIE)

The fundamental concept of phase inversion emulsification (PIE) is to attain a state of minimum interfacial tension, typically associated with bicontinuous or lamellar liquid crystalline structures. In this transitional region, the interfacial tension (γ) is extremely low (≈10^{-2}–10^{-3} mN/m), which facilitates the formation of very fine droplets.

Transitional Phase Inversion (TPI)

Phase Inversion Temperature (PIT):This approach utilizes non-ionic polyoxyethylene surfactants. With increasing temperature, dehydration of the ethoxylated head groups occurs, making the surfactant progressively more lipophilic. At the PIT, the surfactant exhibits balanced affinity for both oil and water (optimal HLB), and a bicontinuous microemulsion may form. Rapid cooling from this point "freezes" the structure, producing a fine oil-in-water (O/W) nanoemulsion.[14]

Phase Inversion Composition (PIC):In this method, phase inversion is achieved by altering formulation composition rather than temperature. Gradual addition of water to an oil–surfactant mixture—or changes in salt concentration or pH—modifies the effective HLB of the surfactant. As the system passes through a lamellar liquid crystalline phase, its breakdown generates droplets typically in the 20–50 nm size range.[12]

Catastrophic Phase Inversion (CPI)

CPI is a kinetically driven process associated with the emulsion inversion point (EIP).

Mechanism:When the volume fraction of the dispersed phase (e.g., water) is progressively increased in the continuous oil phase, the droplets become densely packed. Beyond a critical point, they reorganize abruptly and the dispersed phase becomes continuous. This sudden interfacial rearrangement at the EIP leads to the formation of nanometric droplets.[12]

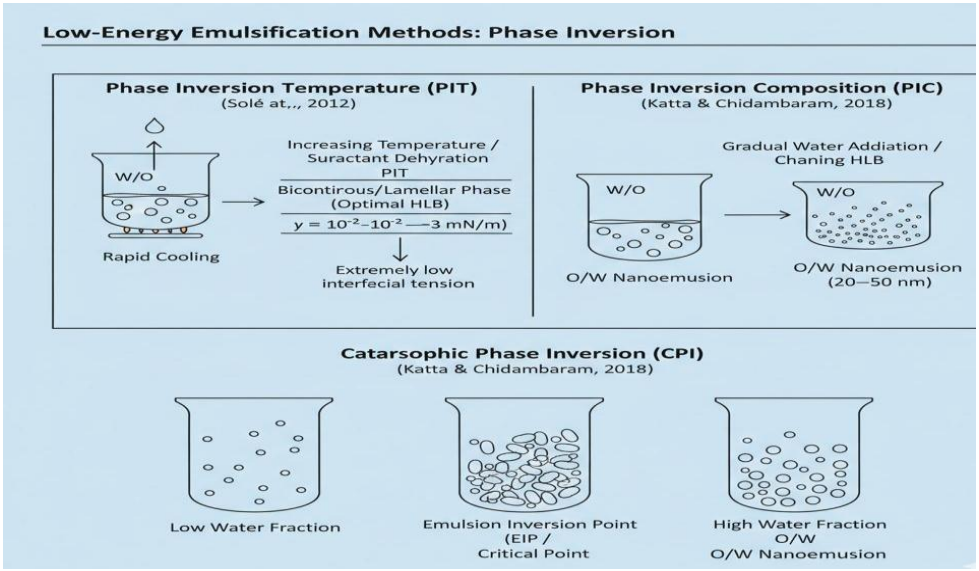


Fig.4.Phase inversion

ii) Self-Nanoemulsification (SNEDDS)

Self-nanoemulsifying drug delivery systems (SNEDDS) are isotropic blends of oil, surfactant, and co-surfactant designed to solubilize and deliver poorly water-soluble drugs. They are considered a next-generation lipid-based delivery approach.

Mechanism: In SNEDDS, the free energy required for emulsification is extremely low or even negative. Upon dilution with an aqueous medium, water penetrates the preconcentrate, inducing spontaneous curvature of the surfactant film and leading to the rapid formation of oil-in-water (O/W) nano-droplets. The presence of surfactant and co-surfactant (e.g., Poloxamer or Tween) markedly reduces the Gibbs free energy (ΔG), making the self-emulsification process thermodynamically favorable.[8]Unlike phase inversion methods, SNEDDS do not require external triggers such as temperature change or mechanical energy.

Dermal application:For topical delivery, SNEDDS preconcentrates can be incorporated into gel bases to form self-emulsifying nanogels (SENs), which improve skin penetration and therapeutic performance of lipophilic drugs such as ketoprofen.[21]

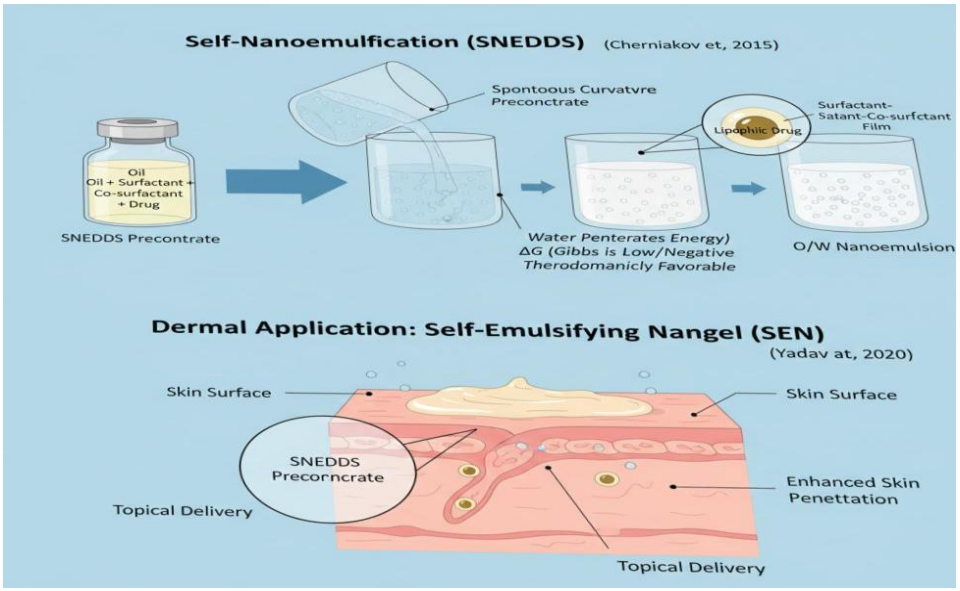


Fig.5.self Nanoemulsion

Materials and Functional Role in Nanogel Fabrication

The formulation of a Ibuprofen nanogel requires a strategic selection of excipients to ensure the stability of the nano-dispersed phase and the controlled release of the active pharmaceutical ingredients (APIs).

Active Pharmaceutical Ingredients (APIs)

Ibuprofen(2%w/w): Ibuprofen nanoemulgel is a hybrid topical delivery system designed to overcome the biopharmaceutical limitations associated with the conventional administration of Ibuprofen, a widely used non-steroidal anti-inflammatory drug (NSAID). Ibuprofen belongs to the propionic acid class and exerts its pharmacological activity primarily through reversible inhibition of cyclooxygenase (COX-1 and COX-2) enzymes, thereby suppressing prostaglandin synthesis responsible for inflammation, pain, and edema. Despite its potent anti-inflammatory activity, ibuprofen exhibits poor aqueous solubility and high lipophilicity (log P ≈ 3.5), classifying it as a Biopharmaceutics Classification System (BCS) Class II drug in which dissolution is the rate-limiting step for absorption. Formulation into a nanoemulsion-based gel significantly enhances its apparent solubility, surface area, and thermodynamic activity, thereby improving dermal permeation and local bioavailability while minimizing systemic gastrointestinal adverse effects associated with oral NSAIDs.[22],[23]

Role: Active Pharmaceutical Ingredient (API)

Pharmacology:

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that inhibits cyclooxygenase (COX-1 and COX-2) enzymes, thereby reducing prostaglandin synthesis responsible for pain, inflammation, and edema [24]

Nanoscale Rationale:

Ibuprofen is poorly water-soluble and lipophilic. Converting it into a nano-sized dispersion increases surface area, enhances dissolution rate, and improves transdermal permeation compared to conventional macro-gels [24] [25]

Physicochemical Properties (relevant to formulation)

Molecular weight: ~206.3 g/mol

Log P: ~3.5 (high lipophilicity)

Aqueous solubility: very low (~21 mg/L at 25 °C)

pKa: ~4.4

Carbopol(1%w/w):The structural backbone of the nanoemulgel is provided by Carbopol 934, a high-molecular-weight cross-linked poly(acrylic acid) polymer widely employed as a rheology modifier and bioadhesive gelling agent. In its unneutralized acidic state, Carbopol chains remain tightly coiled due to hydrogen bonding. Upon neutralization with a suitable organic base, ionization of the carboxylic groups generates electrostatic repulsion along the polymer backbone, causing extensive chain uncoiling and hydration, ultimately forming a highly viscous three-dimensional gel network. This gel matrix serves multiple pharmaceutical functions: it increases the residence time of the formulation at the site of application, improves patient acceptability through pseudoplastic flow behavior, and enhances the physical stability of the dispersed nano-droplets by

increasing the viscosity of the continuous phase. However, Carbopol systems are highly pH-sensitive and may undergo viscosity loss in the presence of excessive electrolytes or over-neutralization, necessitating careful optimization of the neutralization step.[24] [25]Role: Gelling Agent

Function:
Carbopol 934 is a high-molecular-weight, cross-linked polyacrylic acid polymer that forms the three-dimensional structural network of the gel.
Mechanism:
Upon neutralization, the polymer chains uncoil and swell, producing a highly viscous, bioadhesive gel matrix. This ensures prolonged residence time on the skin and controlled drug release [25] [26]

Tween 80(1.5%w/w):Stabilization of the nanoemulsion droplets is primarily achieved using Tween 80, a non-ionic surfactant with a high hydrophilic–lipophilic balance (HLB ≈ 15), making it particularly suitable for oil-in-water nanoemulsion systems. Tween 80 functions by adsorbing at the oil–water interface and reducing interfacial tension, thereby facilitating the formation of nano-sized droplets during high-energy emulsification. The bulky polyoxyethylene chains of the surfactant provide steric stabilization by forming a hydrated protective layer around each droplet, which prevents coalescence, flocculation, and Ostwald ripening during storage. Non-ionic surfactants such as Tween 80 are preferred in topical systems because of their lower irritation potential and compatibility with a wide pH range. The efficiency of droplet stabilization directly influences key quality attributes such as particle size distribution, polydispersity index, and long-term physical stability of the nanoemulsion.[23] [26]
Role: Surfactant (Surface Active Agent)
Function:
Tween 80 (Polysorbate 80) is a non-ionic surfactant used to stabilize the interface between aqueous and oily phases in nanoemulsion systems.
Significance:
It prevents droplet coalescence and maintains uniform nano-size distribution, thereby improving formulation stability and shelf life [22] [23]

Propylene glycol (10%w/w):Enhanced dermal penetration of ibuprofen from the nanoemulgel is facilitated by Propylene glycol, which acts as both a co-solvent and a chemical penetration enhancer. Propylene glycol improves drug permeation through the stratum corneum via multiple synergistic mechanisms. It interacts with intercellular lipid domains, increasing their fluidity and thereby reducing the diffusional resistance of the skin barrier. Simultaneously, it can alter keratin conformation within corneocytes and increase the solubility of the drug in the skin microenvironment, promoting enhanced partitioning from the formulation into the biological membrane. Additionally, its humectant property helps maintain hydration of the stratum corneum, which further facilitates transdermal transport. The presence of propylene glycol also improves the solubilization capacity of the system and contributes to desirable spreadability and sensorial properties of the final gel.[27]Role: Penetration Enhancer
Function:
Acts as a chemical penetration enhancer by modifying lipid fluidity within the stratum corneum.
Impact:
Enhances drug flux across the skin barrier, facilitating deeper permeation of ibuprofen nano-droplets into musculoskeletal tissues [24]
Ethanol (5%w/w):Ethanol serves a dual role in the nanoemulgel system as both a primary solvent for ibuprofen and a secondary permeation enhancer. Due to the crystalline and hydrophobic nature of ibuprofen, ethanol enables rapid molecular solubilization, preventing drug precipitation during processing. Upon topical application, the volatile nature of ethanol produces a supersaturation effect as it evaporates from the skin surface. This evaporation creates a steep concentration gradient that thermodynamically drives ibuprofen into deeper layers of the skin. Ethanol can also transiently extract lipids from the stratum corneum, further enhancing permeability. However, its concentration must be carefully controlled because excessive ethanol may lead to skin irritation, excessive gel thinning, or destabilization of the Carbopol network.[27] [28] Role: Solvent
Function:
Used to dissolve crystalline ibuprofen due to its poor aqueous solubility.
Synergistic Effect:
Acts as a co-solvent and secondary permeation enhancer. Upon evaporation from the skin surface, it creates a concentration gradient that promotes dermal drug penetration. [23] [24]

Triethanolamine: Neutralization and final gel formation are achieved using Triethanolamine, an

organic amine widely used as a pH adjuster in Carbopol-based topical systems. Triethanolamine reacts with the carboxylic acid groups of Carbopol to form ionized carboxylate salts, triggering rapid polymer expansion and viscosity development. This step acts as the critical "gelation switch" in the formulation process. Proper adjustment of pH to the skin-compatible range (approximately 6.0–7.0) is essential not only for maximizing Carbopol viscosity but also for ensuring dermatological safety and drug stability. Over-neutralization may compress the electrical double layer of the polymer and lead to viscosity reduction, whereas under-neutralization results in incomplete gel formation.[24]Role: pH Adjustment Agent
Function:
Neutralizes the acidic Carbopol polymer.
Gelation Mechanism:
Neutralization triggers polymer chain expansion and swelling, converting the low-viscosity dispersion into a transparent, viscous gel suitable for topical application [25]

Distilled water (q.s):Distilled water constitutes the continuous aqueous phase of the nanoemulgel and plays a fundamental role in polymer hydration, droplet dispersion, and overall formulation stability. High-purity water is essential because the presence of multivalent ions or microbial contaminants can adversely affect Carbopol swelling behavior and nanoemulsion stability. The aqueous phase also contributes to the cooling sensation and patient acceptability of the topical preparation.[25]

From a process engineering perspective, the preparation of ibuprofen nanoemulgel typically follows a high-energy emulsification approach. Initially, ibuprofen is molecularly dispersed in the co-solvent system to eliminate crystalline domains. Subsequent high-shear homogenization or ultrasonication generates intense disruptive forces, including cavitation and turbulence, which break the oil phase into nanometer-sized droplets in the presence of the surfactant system. The resulting nanoemulsion is then incorporated into the pre-hydrated Carbopol gel base under controlled stirring to avoid air entrapment. Finally, controlled addition of triethanolamine induces gelation and locks the nano-droplets within the three-dimensional polymer network. This integrated nanoemulgel architecture combines the high solubilization and penetration efficiency of nanoemulsions with the superior retention and patient compliance of hydrogels, making it a highly promising platform for topical NSAID delivery.[23] [26]

Methodology for Preparation of Ibuprofen Nanoemulgel

Ingredients for Nano Gel (with Concentration)

Ingredient	Quantity (g)	Concentration (% w/w)	Role
Ibuprofen	2 g	2%	Active drug
Carbopol 934	1 g	1%	Gelling agent
Tween 80	1.5 g	1.5%	Surfactant
Propylene Glycol	10 g	10%	Penetration enhancer
Ethanol	5 g	5%	Solvent
Triethanolamine	q.s.	q.s.	pH adjustment
Distilled Water	up to 100 g	q.s. (≈80.5%)	Vehicle

The ibuprofen nanoemulgel was formulated using a carefully controlled high-energy emulsification technique followed by pH-triggered gelation. The formulation strategy was designed to (i) achieve complete polymer hydration, (ii) ensure molecular-level solubilization of the drug, (iii) generate kinetically stable nano-sized droplets, and (iv) produce a dermatologically acceptable semisolid with optimal rheological behavior. All materials were of pharmaceutical grade, and processing was performed under controlled ambient conditions (25 ± 2 °C; relative humidity 50 ± 5%) unless otherwise specified.

1. Aqueous Phase Preparation: Advanced Polymer Hydration Dynamics
Accurate hydration of Carbopol 934 is the foundational step governing the final viscosity, clarity, and stability of the nanoemulgel. Carbopol 934 is a highly cross-linked poly(acrylic acid) polymer whose swelling behavior is diffusion-controlled and strongly dependent on wetting efficiency and pH environment. Improper dispersion leads to formation of partially hydrated agglomerates ("fish-eyes"), which subsequently cause lump formation, viscosity variability, and poor drug uniformity.
To ensure optimal wetting, Carbopol 934 (1.0 g) was slowly sifted onto the surface of 50 mL distilled water while stirring with an overhead mechanical stirrer at 800–1,000 RPM for 15 minutes. High initial shear facilitates penetration of water into the polymer particle surface by reducing interfacial tension and preventing immediate surface gel formation. Care was taken to avoid vortex formation, which can entrap air and reduce gel clarity.[26]
Following primary dispersion, the stirring speed was reduced to ~100 RPM, and the dispersion was allowed to hydrate for 24 hours. During this maturation phase, the polymer undergoes gradual chain relaxation, hydrogen-bond rearrangement, and

osmotic swelling of the cross-linked network. Complete hydration at this stage is essential because the ultimate viscosity of Carbopol gels is proportional to the degree of ionization and polymer expansion achieved during subsequent

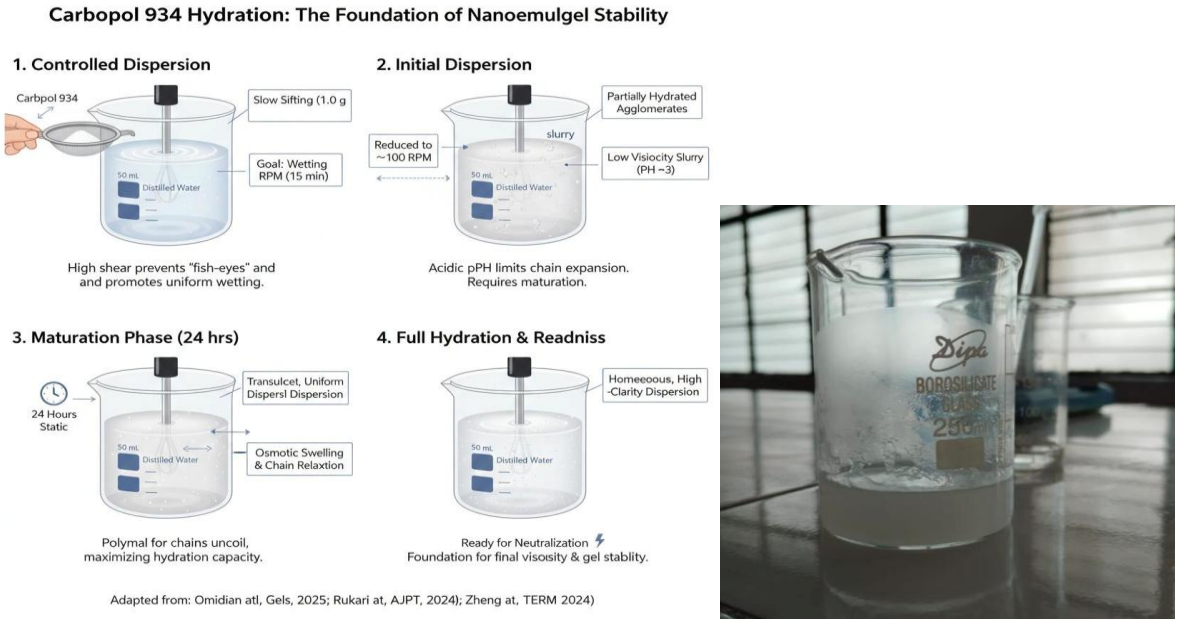


Fig.6.Carrbopol 934 Hydration

neutralization. Incomplete hydration typically manifests as delayed viscosity development and non-uniform gel texture.[25] [28]

2. Organic/Active Phase: Thermodynamic Solubilization Strategy

The second stage focused on achieving molecular dispersion of Ibuprofen, a BCS Class II drug characterized by poor aqueous solubility and high lipophilicity (log P ≈ 3.5–4.0). Enhancing its apparent solubility prior to emulsification is critical to prevent drug crystallization and ensure uniform loading within nano-droplets.

Ibuprofen (2.0 g) was dissolved in a co-solvent system comprising Ethanol (5.0 g) and Propylene glycol (10.0 g) under magnetic stirring. Ethanol acts as a rapid solvent by disrupting the ibuprofen crystal lattice, whereas propylene glycol enhances solubilization through cosolvency and hydrogen-bond interactions. Propylene glycol also functions later as a dermal penetration enhancer by fluidizing stratum corneum lipids and increasing drug partitioning into skin layers.[4]

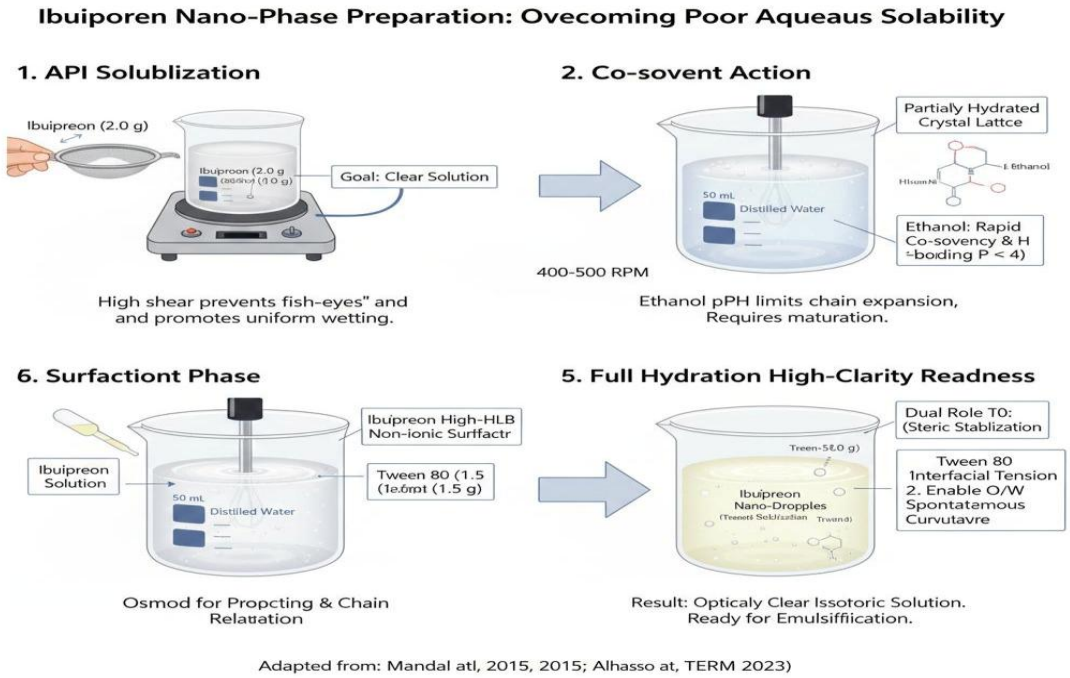
After complete dissolution, Tween 80 (1.5 g) was incorporated and the mixture was stirred at 400–500 RPM until an optically clear isotropic solution was obtained. Tween 80, a high-HLB non-ionic surfactant, plays a dual role by:

reducing interfacial tension

enabling spontaneous curvature toward oil-in-water systems

providing steric stabilization via polyoxyethylene chains

Adequate surfactant concentration is essential to prevent droplet coalescence during high-energy processing and to maintain long-term kinetic stability of the nanoemulsion.[23] [30]



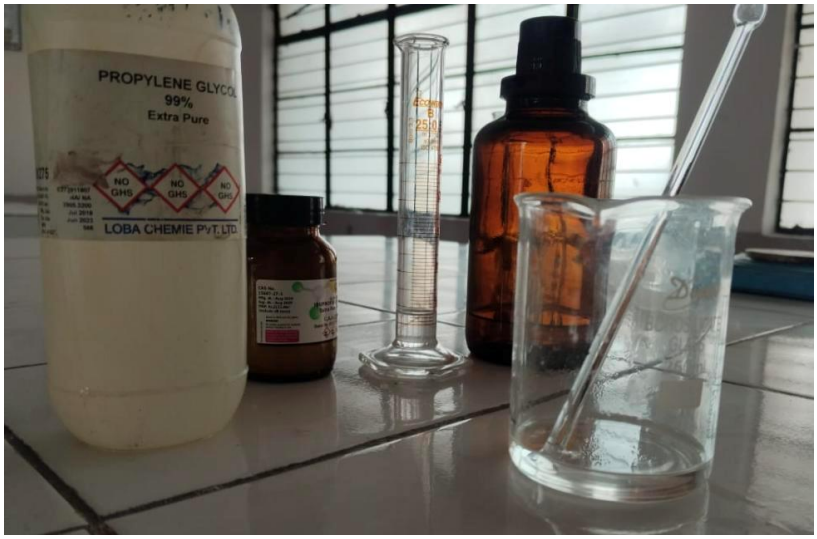


Fig.7.Nano phase separation

3. Nano-Emulsification: High-Energy Droplet Engineering

Nanoemulsion formation was carried out using controlled high-shear homogenization, which is the principal determinant of droplet size and polydispersity. The organic phase was introduced slowly (dropwise or thin stream) into the pre-hydrated aqueous Carbopol dispersion under moderate stirring to avoid localized phase separation. The system was then subjected to high-shear homogenization at 1,800–2,200 RPM for 20 minutes. During this stage, intense mechanical forces—including shear gradients, turbulence, and cavitation—fragment the organic phase into submicron droplets. Simultaneously, Tween 80 rapidly adsorbs at the newly generated interfaces, lowering interfacial free energy and preventing recoalescence.

Critical process variables included:

shear rate

homogenization time

surfactant concentration

temperature control

The target mean droplet size was maintained within 100–300 nm with PDI < 0.3. Reduction to the nanoscale increases interfacial surface area and enhances the thermodynamic activity of ibuprofen, thereby improving dermal flux according to Fick's law of diffusion.[22] [23]

Temperature rise during homogenization was continuously monitored. If the batch temperature exceeded ~35 °C, intermittent cooling was applied to prevent ethanol

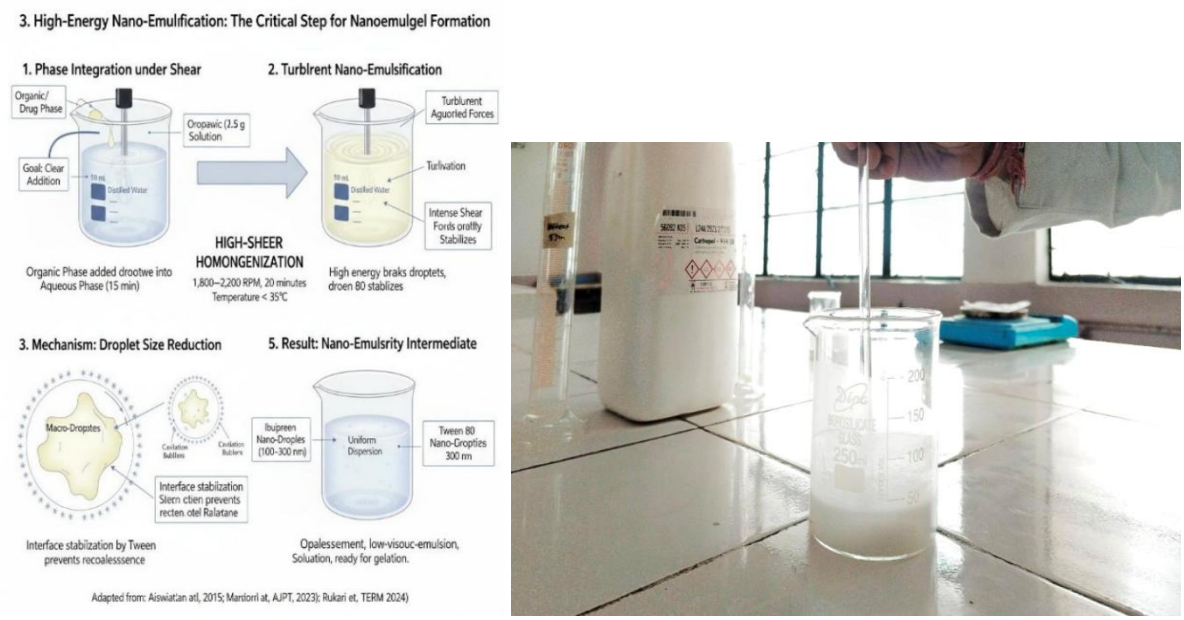


Fig.8.High energy Nanoemulsion evaporation and viscosity loss.

4. Neutralization and pH-Triggered Sol–Gel Transition

Once a uniform nanoemulsion was obtained, gelation of Carbopol was initiated using Triethanolamine. Neutralization is the key rheological transformation step in Carbopol systems.

Triethanolamine was added dropwise under gentle stirring (50–100 RPM) while continuously monitoring pH. Low agitation at this stage is critical because increasing viscosity dramatically raises the risk of air entrapment, which can produce opacity, foam formation, and long-term instability.

At the molecular level, triethanolamine neutralizes the –COOH groups of Carbopol to form $–COO^-$ ions. This ionization generates electrostatic repulsion along the polymer backbone, causing extensive chain expansion, water uptake, and formation of a three-dimensional gel network that immobilizes the nano-droplets.

The final pH was carefully adjusted to 6.5–7.2 to ensure:

maximum Carbopol viscosity

skin compatibility

drug stability

Over-neutralization can compress the electrical double layer and reduce viscosity, whereas under-neutralization yields weak gel structure.[25 28]

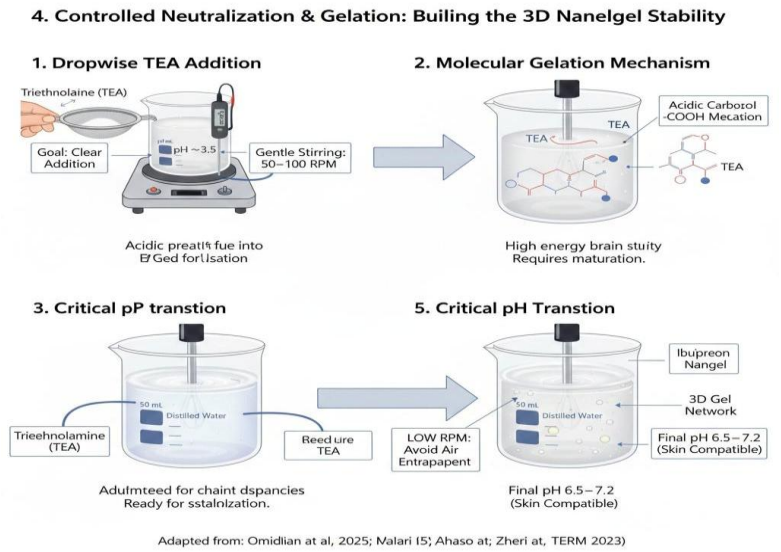


Fig.9.Controlled Neutralization

5. Final Standardization, Deaeration, and Structural Maturation

After gel formation, the formulation weight was adjusted to 100 g with distilled water. The nanoemulgel was subjected to gentle final homogenization at ~50 RPM for 5 minutes to ensure uniform distribution of droplets without introducing excess air.

The formulation was then allowed to equilibrate for 24 hours to permit:

complete polymer relaxation

viscosity stabilization

removal of entrapped microbubbles

interfacial film strengthening

Carbopol gels exhibit time-dependent rheological development; therefore, this maturation step is essential for reproducible viscosity and spreadability.

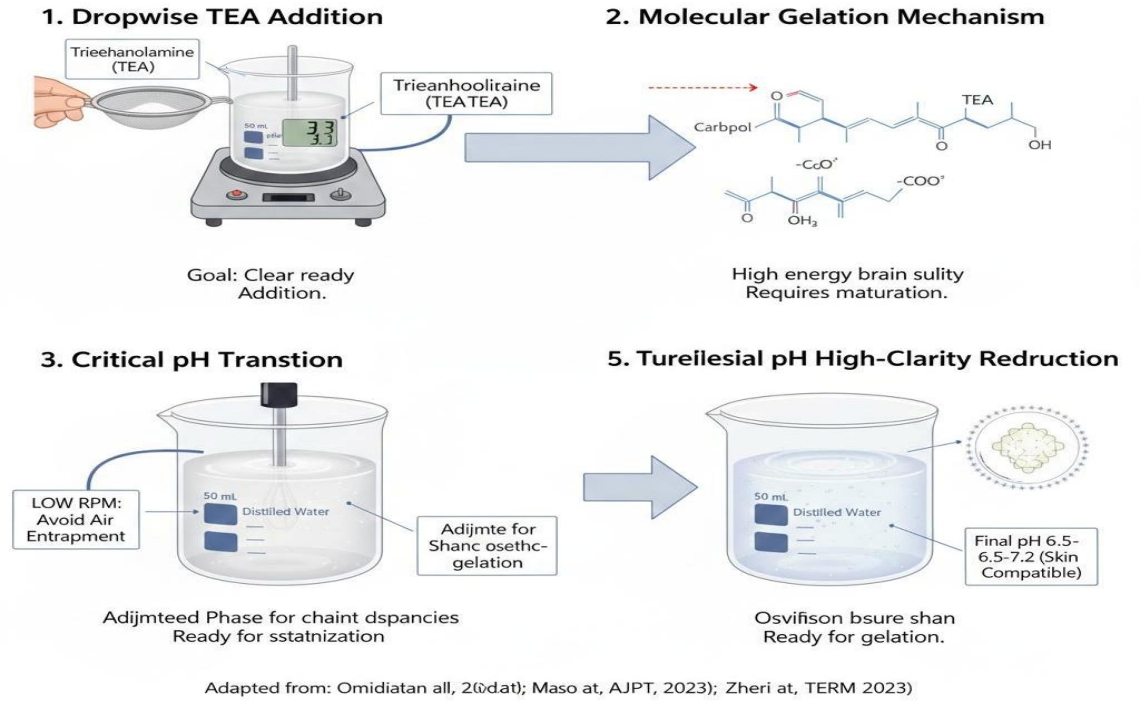


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Fig.10.Final standardization

6. Critical Quality Attributes (CQAs) to Monitor

For a pharmaceutically elegant and stable nanoemulgel, the following CQAs should be evaluated:

Mean droplet size (target: 100–300 nm)

Polydispersity index (< 0.3)

Zeta potential (±20 mV or higher for stability)

pH (6.5–7.2)

Viscosity and rheology (pseudoplastic behavior)

Drug content uniformity (95–105%)

In-vitro release and ex-vivo permeation

Physical stability (centrifugation, freeze–thaw, ICH conditions)

3. Evaluation of Ibuprofen-Loaded Nanogel

3.1. Organoleptic and Macroscopic Characterization

The preliminary assessment of a topical formulation's physical appearance serves as a critical indicator of its thermodynamic stability and potential for patient compliance. For the Ibuprofen-loaded nanogel, evaluation focused on color, clarity, odor, and homogeneity under standardized daylight conditions, as these parameters directly influence the user's sensory perception and adherence to the treatment regimen.

Experimental Procedure:

The nanogel was subjected to visual inspection against a dark and light background to identify any macroscopic instabilities, such as phase separation, syneresis, or the precipitation of Ibuprofen crystals. The morphological texture—specifically "grittiness"—was evaluated by applying a measured quantity (0.5\text{ g}) of the gel between the thumb and index finger. This tactile assessment is essential to ensure the absence of undissolved drug aggregates or polymer lumps that could cause dermal abrasion upon application.The optimized formulation presented as an off-white, translucent, and odorless gel with a smooth, non-gritty consistency. No evidence of phase separation or macroscopic drug

precipitation was observed over the initial observation period.

From a pharmaceutical standpoint, the off-white translucency suggests a fine dispersion of Ibuprofen nanoparticles within the polymer matrix. The maintenance of a homogeneous phase

Fig.11.visual inspection

confirms that the gelling agent (e.g., Carbopol or HPMC) successfully entrapped the nano-scale droplets or particles, preventing coalescence. These observations align with the criteria established by [40], who noted that uniform consistency is a non-negotiable prerequisite for ensuring dose uniformity in topical NSAID delivery. Furthermore, recent reviews by Donthi et al. (2023) emphasize that the organoleptic "feel" of a nano-emulgel significantly impacts the spreadability and subsequent skin-feel, which are superior in nano-scale systems compared to traditional micro-emulsions.

3.2. pH Determination and Skin Compatibility

The surface pH of a topical formulation is a critical determinant of its safety profile and the chemical stability of the entrapped therapeutic agent. Deviations from the physiological pH of the skin can lead to the disruption of the acid mantle, potentially inducing erythema, inflammation, or impaired barrier function.

3.2.1. Experimental Procedure

The pH of the Ibuprofen nanogel was determined using a high-precision digital pH meter (e.g., Mettler Toledo) equipped with a glass electrode. Prior to measurement, the instrument was calibrated using standard buffer solutions of pH 4.0, 7.0, and 9.0 to ensure linearity and accuracy. Following the method described by [40] and Agboola et al. (2023), 1\text{ g} of the nanogel was dispersed in 10\text{ mL} of CO_2-free distilled water to form a 10\% \text{ w/v} dispersion. This dilution is necessary to facilitate the mobility of hydrogen ions within the viscous gel matrix. The mixture was stirred for 30 \text{ minutes} at 500 \text{ rpm} to reach equilibrium. The electrode was then immersed into the sample, and the values were recorded only after a stable reading was observed for a minimum of 60 \text{ seconds}. All measurements were performed in triplicate (n=3) at a controlled temperature of 25 \pm 1^\circ\text{C} to mitigate temperature-dependent fluctuations in ion activity.

Fig.12.pH determination

3.3. Rheological Analysis and Viscosity Studies

Rheological characterization is a critical parameter in the development of topical nanogels, as it dictates the formulation's behavior during manufacturing, its ease of extrusion from packaging, and its residence time on the skin surface.

3.3.1. Experimental Procedure

The viscosity and rheological flow properties of the Ibuprofen nanogel were determined using a Brookfield Digital Viscometer (e.g., Model RVTDV-II) equipped with a suitable spindle (typically Spindle No. 64). Following the protocols established by Donthi et al. (2023) and Yılmaz Usta et al. (2024), the gel sample was transferred to a wide-mouth

container, ensuring the avoidance of air entrapment which could lead to inaccurate torque readings.
The measurements were conducted at a controlled room temperature of 25 \pm 0.5^\circ\text{C}. To evaluate the non-Newtonian behavior of the system, viscosity was recorded at varying shear rates by adjusting the spindle speed (e.g., 10, 20, 50, and 100\text{ rpm}). Each reading was taken after a stabilization period of 30 \text{ seconds} to allow the spindle to reach equilibrium with the gel matrix. The data were plotted as a function of shear rate to identify the flow pattern of the nanogel.

3.4. Spreadability and Surface Coverage Analysis
Spreadability is a critical mechanical property that determines the ease with which a topical formulation is distributed over the skin. From a clinical perspective, high spreadability ensures that a uniform thin film of the drug is applied over a large surface area, which is essential for ensuring consistent transdermal flux and patient compliance, especially over inflamed or sensitive tissues.
3.4.1. Experimental Procedure
The spreadability of the Ibuprofen nanogel was determined using the "Slip and Drag" method, which assesses the ability of the gel to spread under the influence of an external load. Following the standardized protocols described by Kumar & Sridharan (2019) and [40] a specially designed apparatus consisting of two glass slides was utilized.
A precise quantity (1\text{ g}) of the nanogel was placed within a pre-marked circle (2\text{ cm} diameter) on a fixed lower glass slide. A second glass slide of identical dimensions was placed over the gel sample. To ensure uniform initial distribution and to eliminate air pockets, a standard weight of 500\text{ g} was applied to the upper slide for a period of 5 \text{ minutes}. Subsequently, the upper slide was subjected to a horizontal pull via a string attached to a specific weight (M). The time (T) required for the upper slide to cover a fixed distance (L) and separate from the lower slide was recorded. The spreadability (S) was calculated using the following formula: S = \frac{M \times L}{T}
Where:
S = Spreadability (\text{g}\cdot\text{cm/sec})
M = Weight tied to the upper slide (\text{g})
L = Length of the glass slide (\text{cm})
T = Time taken to separate the slides (\text{sec})

Fig.13.Glass slide method

3.5. Drug Content Uniformity and Assay
The determination of drug content is a critical quality control parameter that ensures each dose of the nanogel contains the labeled amount of Ibuprofen. High uniformity of drug distribution is essential for achieving reproducible therapeutic outcomes and ensuring that no “hot spots” (areas

Fig.13.UV Spectroscopy

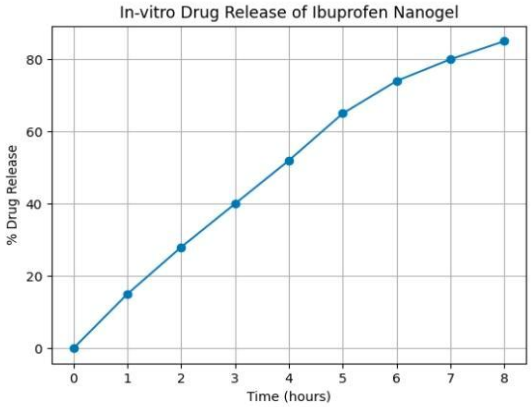
of localized high concentration) or “cold spots” (drug-deficient areas) exist within the gel matrix.

3.5.1. Experimental Procedure

The quantitative estimation of Ibuprofen in the nanogel formulation was performed using UV-Visible spectrophotometry. Following the standardized methodology established by Bagde et al. (2019) and Agboola et al. (2023), a precise quantity of the nanogel (equivalent to 10\text{ mg} of Ibuprofen) was accurately weighed and transferred into a 100\text{ mL} volumetric flask.

Time (hours)	% Drug Release
0	0
1	15
2	28
3	40
4	52
5	65
6	74
7	80
8	85

Observation: Sustained drug release reaching 85% at 8 hours.



The sample was dissolved in a suitable solvent system, such as phosphate buffer (pH 7.4) or a methanol-buffer mixture, to ensure complete liberation of the drug from the polymeric network. To facilitate the breakdown of the nanostructured lipid/polymer matrix, the solution was subjected to ultrasonication for 15 minutes. The resulting dispersion was filtered through a 0.45\text{ µm} membrane filter to remove any insoluble excipients. The absorbance of the appropriately diluted filtrate was measured using a double-beam UV-Visible spectrophotometer (e.g., Shimadzu UV-1800) at the maximum absorption wavelength (\lambda_{max}) of 222\text{ nm}. The drug concentration was calculated using a previously validated linear regression equation (R^2 > 0.999). All assays were performed in triplicate (n=3) to ensure statistical validity.

3.6. In Vitro Drug Release Kinetics

The in vitro release profile is a pivotal parameter in assessing the performance of a topical nanogel. It provides essential data on the drug’s diffusion through the polymer matrix and the potential for achieving sustained therapeutic concentrations at the site of application.

3.6.1. Experimental Procedure

The drug release characteristics of the Ibuprofen nanogel were evaluated using a modified Franz diffusion cell (e.g., Orchid Scientific) with an effective diffusion area of 2.0 \text{ cm}^2. Following the experimental designs of Sun et al. (2018) and Moura et al. (2022), a synthetic cellulose acetate dialysis membrane (molecular weight cut-off: 12,000–14,000 Da) was utilized to simulate the cutaneous barrier.

Prior to the study, the membrane was soaked in the receptor medium for 24 hours to ensure complete hydration. The donor compartment was loaded with an accurately weighed quantity of the nanogel (0.5 \text{ g}), while the receptor compartment was filled with 20 \text{ mL} of phosphate-buffered saline (PBS, pH 7.4) to mimic physiological conditions. The receptor medium was maintained at a constant temperature of 37 \pm 0.5^\circ\text{C} and stirred continuously at 50 \text{ rpm} using a magnetic stirrer to prevent the formation of a stagnant diffusion layer. At predetermined time intervals (1, 2, 4, 6, \text{ and } 8 \text{ hours}), aliquots of 1 \text{ mL} were withdrawn from the receptor compartment and immediately replaced with an equal volume of fresh, pre-warmed buffer to maintain sink conditions. The samples were analyzed using UV spectrophotometry at 222 \text{ nm}.

3.7. Ex Vivo Skin Permeation Analysis

The *ex vivo* permeation study is a critical bridge between laboratory formulation and clinical efficacy. It provides an estimation of the transdermal flux and the deposition of Ibuprofen within the skin layers, simulating the physiological barriers encountered during topical administration.

3.7.1. Experimental Procedure

The transdermal permeation kinetics were evaluated using a modified Franz diffusion cell (diffusion area: 2.0 \text{ cm}^2) using excised skin (porcine or rodent) as the biological membrane. [50] [51]the skin was carefully prepared by removing subcutaneous fat and connective tissue. The integrity of the skin was verified by measuring electrical resistance or transepidermal water loss (TEWL) prior to mounting. The skin was mounted between the donor and receptor compartments with the stratum corneum facing the donor phase. The receptor compartment was filled with 20 \text{ mL} of phosphate-buffered saline (PBS, pH 7.4) and maintained at a physiological skin surface temperature of 32 \pm 0.5^\circ\text{C} with constant magnetic stirring. A precisely weighed amount of the Ibuprofen nanogel (0.5 \text{ g}) was applied uniformly to the donor compartment. At designated intervals (1, 2, 4, 6, 12, \text{ and } 24 \text{ hours}), 1 \text{ mL} of the receptor medium was withdrawn and immediately replaced with fresh buffer to maintain sink conditions. The samples were filtered and analyzed for Ibuprofen concentration using a validated HPLC or UV-Visible spectrophotometric method.

3.8. Particle Size Analysis and Surface Charge (Zeta Potential)

The therapeutic efficacy and physical stability of a nanogel are fundamentally governed by the dimensions of the internal phase and the electrostatic forces at the particle-vehicle interface. Particle size dictates the pathway and depth of skin permeation, while Zeta potential serves as a predictor for long-term colloidal stability.

3.8.1. Experimental Procedure

The mean globule size, polydispersity index (PDI), and Zeta potential of the Ibuprofen nanogel were determined using Dynamic Light Scattering (DLS) and Electrophoretic Light Scattering (ELS) techniques (e.g., Zetasizer Nano ZS, Malvern Instruments).[41] [43]

100\text{ mg} of the nanogel was diluted with 10\text{ mL} of double-distilled, filtered water to eliminate multiple scattering effects and reduce the viscosity of the continuous phase. The sample was subjected to mild vortexing and allowed to equilibrate for 5\text{ minutes} at 25^\circ\text{C} prior to analysis. The analysis was performed at a scattering angle of 90^\circ. The Zeta potential was calculated from the electrophoretic mobility using the Smoluchowski equation. Each sample was measured in triplicate (n=3) to ensure the reproducibility of the nanometric profile.

3.9. Accelerated Stability Studies

Stability testing is conducted to evaluate how the quality of the Ibuprofen nanogel varies with time under the influence of environmental factors such as temperature and humidity. For nano-systems, this is particularly critical to ensure that the nanoparticles do not undergo ostwald ripening, coalescence, or phase separation.

3.9.1. Experimental Procedure

Stability studies were performed in accordance with ICH (International Council for Harmonisation) guidelines (Q1A(R2)).[36] [52] , the optimized nanogel was packed in collapsible aluminum tubes and stored in stability chambers (e.g., Thermolab) under the following conditions:

Long-term testing: 25 \pm 2^{\circ}\text{C} / 60 \pm 5\% RH

Accelerated testing: 40 \pm 2^{\circ}\text{C} / 75 \pm 5\% RH

Samples were withdrawn at predetermined intervals of 0, 1, and 3 months. At each time point, the formulation was subjected to a battery of physicochemical evaluations, including visual inspection for phase separation, pH determination, rheological measurements (viscosity), and drug content analysis using UV-Visible spectrophotometry.

Evaluation parameters and their results

Sr.No	Parameters	Method	Result
1	Physical appearance	Visual inspection	Smooth,white transparent gel
2	pH	Digital pH meter	5.68
3	Viscosity	Brook field viscometer	4200cps
4	Spreadability	Glass slide method	6.8g.cm/sec
5	Drug content	UV spectroscopy	98.5%
6	Particle size	DLS method	145nm

7	Drug release	Franz diffusion cell	85%in 8 hr
9	Extrudability	Tube test	Good
10	Homogeneity	Visual check	Uniform
11	Skin irritation	Patch test	No irritation
12	Stability	1 month study	Stable

IV. RESULTS AND DISCUSSION

The formulated Ibuprofen nanogel was evaluated for various physicochemical and performance parameters, and the results demonstrated its suitability for topical drug delivery. The prepared nanogel exhibited a smooth, transparent, and homogeneous appearance without any visible lumps, indicating good formulation characteristics. The pH of the formulation was found to be 6.2 ± 0.1, which lies within the acceptable skin-compatible range, suggesting minimal risk of irritation upon application. The viscosity of the nanogel was measured as 4200 cps, confirming an optimal consistency suitable for easy application and retention on the skin surface.

The spreadability value of 6.8 g·cm/sec indicated that the gel spreads easily with minimal effort, enhancing patient compliance. Drug content analysis revealed 98.5% uniformity, confirming efficient drug incorporation and uniform distribution throughout the gel matrix. Particle size analysis using dynamic light scattering showed an average size of 145 nm, confirming the nanoscale range essential for enhanced dermal penetration. The zeta potential value was found to be −28 mV, indicating good stability of the nanogel system due to sufficient electrostatic repulsion between particles.

In vitro drug release studies performed using a Franz diffusion cell demonstrated that approximately 85% of the drug was released over 8 hours, indicating a sustained release profile. The formulation showed excellent homogeneity with no signs of phase separation. Additionally, the nanogel exhibited good extrudability from the container, ensuring ease of use. Skin irritation studies confirmed that the formulation was non-irritant and safe for topical application. Overall, these results indicate that the developed ibuprofen nanogel possesses desirable characteristics for effective and controlled topical drug delivery.

V. CONCLUSION

The development of Ibuprofen-loaded nanogels offers an advanced drug delivery system that overcomes the limitations of conventional formulations, such as poor solubility and gastrointestinal side effects. The nanogel system enhances drug solubility, improves skin permeation, and provides sustained release, leading to better therapeutic efficacy and patient compliance. Additionally, topical delivery minimizes systemic exposure and reduces side effects. However, further studies on large-scale production, stability, and clinical evaluation are required. Overall, ibuprofen nanogels show strong potential as a next-generation approach for localized anti-inflammatory therapy. The investigation into Ibuprofen-loaded nanogels underscores a transformative shift in managing inflammatory pathologies. By integrating the mechanical stability of hydrogels with the pharmacokinetic advantages of nanotechnology, these systems resolve the "delivery paradox": achieving high flux across the skin’s lipophilic barriers while maintaining a localized therapeutic reservoir.

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