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Review Article

Nanoemulgel: A Comprehensive Review on Recent Advances in Topical Drug Delivery Systems

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Abstract

Nanoemulgels represent a significant advancement in topical drug delivery, particularly for lipophilic compounds characterised by poor aqueous solubility and low oral bioavailability. By integrating oil-in-water (o/w) nanoemulsions—typically featuring droplet sizes between 10 and 200 nm—into a structured hydrogel matrix, this system merges the high-penetration capabilities of nanotechnology with the favourable rheological properties of a gel. Unlike conventional creams or ointments, which are often hindered by greasiness and low spreadability, nanoemulgels provide a non-greasy, bio-adhesive alternative that improves patient compliance. Functionally, this delivery system bypasses first-pass metabolism and gastrointestinal degradation, delivering therapeutic agents directly to the target site. This localised approach is highly effective for treating inflammatory and infectious conditions such as rheumatoid arthritis, psoriasis, and fungal infections. The presence of surfactants and gelling agents enhances skin permeability by temporarily modifying the lipid barrier, facilitating both immediate and sustained drug release. As pharmaceutical research trends toward increasingly hydrophobic molecules, nanoemulgels stand as a superior, biocompatible standard for efficient, site-specific therapy.

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INTRODUCTION

While standard topical treatments like creams and ointments have been the go-to for decades, they come with a set of "behind-the-scenes" frustrations for both scientists and patients. One of the biggest hurdles is a fundamental chemistry mismatch: many of today's most effective medications are lipophilic (oil-loving), which makes them notoriously difficult to dissolve in water-based formulas. This often leads to uneven absorption, meaning the drug doesn't always work as reliably as it should. Beyond the chemistry, there is the physical challenge of the skin itself. The stratum corneum, our skin's outermost layer, is an incredibly effective natural shield. While its job is to keep toxins out, it is often too good at its job, acting as a barrier that prevents active ingredients from penetrating deep enough to reach the underlying tissue where they are actually needed.[1,2,3]

Nanoemulgels are a clever solution to a common problem in skincare and medicine: how to get oily ingredients to absorb into the skin without leaving a greasy mess. By blending a nanoemulsion (tiny oil droplets) into a hydrogel (a water-based gel), scientists have created a "best of both worlds" system. The Nano emulsion part acts as a delivery vehicle, using incredibly small droplets—often smaller than a skin pore—to dissolve and carry ingredients that usually don't mix with water. However, because these emulsions are often thin and runny, they are hard to apply. That is where the hydrogel comes in. It provides the "body" or thickness needed to make the formula easy to spread and helps it stick to the skin longer, ensuring the active ingredients have enough time to do their work effectively.[4,5,6]

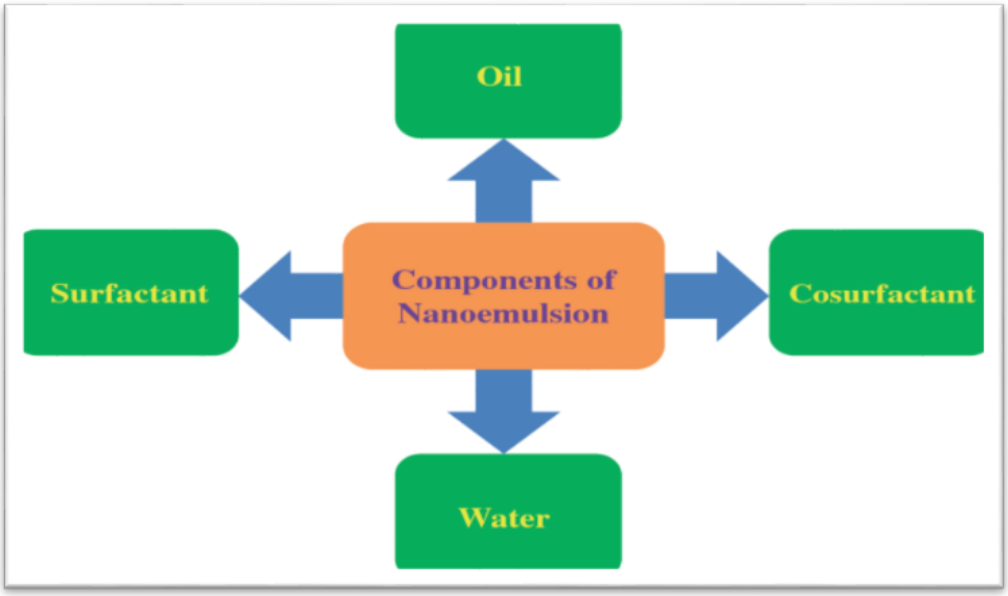
Nanoemulgels have become a top priority in modern medical research because they offer a smarter way to deliver medications through the skin. One of their biggest advantages is the ability to bypass the digestive system and liver metabolism, which often break down drugs before they can even start working. For example, when the anti-inflammatory drug flurbiprofen is applied as a Nanoemulsion, it can be up to 4.4 times more effective than taking the same medication as an oral pill.[12]

The secret to this success lies in its hybrid design. The gel acts like a stable reservoir, slowly releasing the medication over time, which is perfect for drugs that usually wear off quickly in the body[13]. Beyond just being more effective, the thick consistency of the gel prevents the formula from separating or spoiling, making it much more shelf-stable than standard creams. Because the droplets are so microscopic, they can travel through multiple pathways in the skin, ensuring the medicine penetrates deeper and works more efficiently than traditional ointments.[14]

The therapeutic scope of Nanoemulgels has expanded significantly beyond traditional anti-inflammatory applications to address complex medical and aesthetic challenges. In dermatology, these systems provide targeted relief for chronic conditions such as acne, psoriasis, and various fungal infections by ensuring deeper follicular penetration. Beyond localised treatment, they are being pioneered for systemic diseases, including novel "nose-to-brain" pathways for Parkinson's disease and advanced follicular delivery for alopecia. Furthermore, the cosmeceutical industry has adopted nanoemulgels to enhance UV protection and accelerate skin repair, leveraging their superior stability and non-greasy texture to improve both efficacy and patient adherence.

Components of Nanoemulsion

Fig.No.1: Components of Nanoemulsion



Oil Phase

In Nanoemulgels formulations, the oil phase acts as the essential "home" for medications that cannot dissolve in water. By carefully choosing an oil that naturally blends with the drug, scientists can pack more of the active treatment into the formula while keeping it stable. These microscopic oil droplets are then tucked into a smooth gel, which transforms a runny liquid into a creamy, easy-to-apply treatment that stays on the skin longer and helps the medicine penetrate deeper for better healing. [15,16]

Surfactants

Are surface active agents. They are an essential ingredient in nano-emulsions, which are utilised in the stabilisation of the unstable mix of two immiscible phases. This is achieved by decreasing the interfacial tension between the two phases and altering the dispersion entropy. The surfactant should show quick adsorption along the interface of the liquids. The final result is a decrease in interfacial tension and inhibition of coalescence of the individual Nano-sized droplets [8]

Scientists are increasingly looking toward nature—specifically bacteria, fungi, and animals—to find the next generation of surfactants. These "bio-surfactants" are gaining traction because they align better with our health and the environment, offering a level of safety, biodegradability, and biocompatibility that traditional lab-made chemicals often lack. At a molecular level, these natural compounds work much like their synthetic counterparts to break down surface tension. Their effectiveness comes from an "amphiphilic" design, meaning they have two distinct personalities: a non-polar "tail" made of short fatty acids that avoids water, and a polar "head" that thrives in it. This dual nature allows them to sit perfectly at the interface of different substances, like oil and water, to bridge the gap between them. Because they are derived from living organisms, they are generally gentler on human skin and more eco-friendly, making them a superior, "greener" alternative to the harsh synthetic surfactants we've relied on in the past.[18]

Co Surfactants

To further stabilise an emulsion's interfacial film and prevent droplets from merging, co-surfactants are added as essential excipients. To determine the solubility of a drug in various co-surfactants, an excess amount of the substance is added to 5 mL of selected candidates—such as PEG 400, PEG 200, and Propylene Glycol (PG)—within 15 mL stoppered vials.

These mixtures are then placed in a rotary shaker and maintained at a constant temperature of 37 ± 1.0°C for 72 hours to ensure they reach equilibrium. Once the saturation period is complete, the samples are centrifuged at 3000 rpm for 15 minutes to separate any undissolved material. Finally, the resulting supernatant is filtered, and the concentration of the dissolved drug is measured using a UV Spectrophotometer.

Gelling agent

In the world of topical treatments, nanoemulsions are highly valued for their tiny droplet size—usually between 10 and 200 nm—which allows them to carry medicine deep into the skin. However, because these emulsions are essentially watery liquids, they are difficult to apply and tend to run off the skin too quickly. This is where a gelling agent comes in. It acts as the structural backbone of the formula, turning a thin liquid into a stable, easy-to-spread "nanoemulgel." By creating an invisible 3D mesh, the gelling agent traps the tiny oil droplets in place. This not only makes the product stay on the skin longer but also prevents the droplets from clumping together, ensuring the medicine stays effective until the moment it's used[19].

Choosing the right gelling agent is a major focus for researchers. Synthetic polymers, like the Carbopol series, are incredibly popular because they create crystal-clear gels that feel premium and stick well to the skin. If a more "natural" or biocompatible approach is needed, semi-synthetic celluloses (like HPMC or CMC) are often used because they are gentle on the skin and form a protective film. Recently, there has been a shift toward natural biopolymers like Xanthan gum or Chitosan. Chitosan is particularly interesting because its natural positive charge helps it "grip" the skin better and can even help fight bacteria, making it a dual-purpose ingredient[20].

When reviewing these agents, scientists look at more than just thickness; they look at the "feel" and performance. A good gel should exhibit shear-thinning, which means it stays thick in the bottle but becomes fluid and easy to spread the moment you rub it onto your skin. It also needs to be compatible with the skin's natural, slightly acidic pH (5.5) to prevent irritation. Finding the right balance is key: too much gelling agent creates a wall that traps the medicine inside, while too little results in a messy, unstable product. Ultimately, the gelling agent is what bridges the gap between high-tech lab science and a product that a patient can actually use comfortably and effectively.[21]

Table 1: Comparison of Nanoemulgel and Nanoemulsion Parameters

Parameters	Nano-emulgel	Nano-emulsion
Method of Preparation	Low-energy method	High-energy method
Particle size	Less than 100 nm	Greater than 500 nm
Thermodynamic stability	More stable	Less stable due to sedimentation
Permeation	High permeation due to particle size	Lower permeation
Bioavailability	High	Less in comparisons
Systemic absorption	High	Low in comparison to gel
Ability to cross BBB	Cross BBB	Less in comparison gel

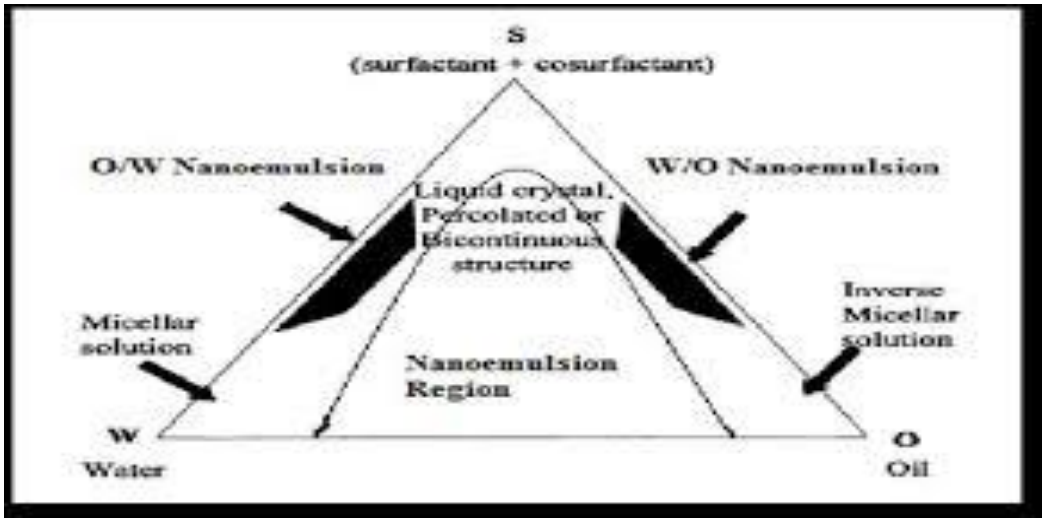
Method of preparation

Pseudo Ternary Phase Diagram

In the development of nanoemulsions, the pseudo-ternary phase diagram acts as a strategic map that helps researchers identify the exact "sweet spot" where oil, water, and surfactants blend into a stable, clear mixture. Because these systems typically involve four ingredients—oil, water, a surfactant, and a co-surfactant—it would normally require a complex 3D model to track them all. To simplify this, scientists use a "pseudo" ternary approach by grouping the surfactant and co-surfactant into a single, fixed-ratio blend known as the S_{mix}. This allows the formulation to be plotted on a two-dimensional equilateral triangle. The ultimate goal of this mapping is to highlight the "nanoemulsion region," which is the specific area on the graph

where the ingredients spontaneously organise into tiny droplets, usually smaller than 200 nm.[12]

Fig. No. 2 Pseudo Ternary Phase Diagram



The Aqueous Titration Process

The most practical way to build this diagram is through a technique called aqueous titration, often referred to as spontaneous emulsification. In the lab, this begins by mixing the oil and the S_{mix} in various weight ratios—ranging from 1:9 to 9:1—within small glass vials. Once these organic phases are thoroughly blended, the researcher slowly adds the aqueous phase (water) drop by drop while gently stirring or vortexing the mixture. After each addition, the vial is checked for visual changes: a clear, transparent appearance indicates a stable Nano emulsion, while a cloudy or "milky" look suggests the droplets are too large or unstable.[22,23]

By recording exactly when the mixture flips from clear to turbid, scientists can mark the boundaries of the stable zone on the diagram. For those designing a topical Nanoemulsion, the ideal formula is usually chosen from the centre of this identified stable region. Picking a point in the middle ensures that the emulsion is robust enough to stay together even after a gelling agent is added to give it that final, easy-to-apply consistency.

The Gelation Process: Creating the Nanoemulgel

The transformation of a liquid nanoemulsion into a nanoemulgel is a deliberate, multi-step process often called the "incorporation" or "thickening" method. This technique essentially bridges the gap between high-tech liquid drug delivery and a user-friendly topical product. It begins by preparing two separate systems: the primary nanoemulsion (which holds the medicine) and a dedicated hydrogel base. To create the gel base, polymers like Carbopol, HPMC, or Xanthan Gum are dispersed in purified water. This stage requires patience; the polymer must be allowed to fully hydrate and swell—often for up to 24 hours—to avoid any lumps. If using Carbopol, a neutralising agent like Triethanolamine is added to adjust the pH, causing the tightly coiled polymer chains to spring open and instantly thicken the water into a crystal-clear, viscous gel.[24]

Once both parts are ready, the actual gelation occurs by merging them. The liquid nanoemulsion is slowly poured into the hydrogel base while maintaining constant, gentle stirring. This is a delicate balancing act for the formulator: the mixing must be thorough enough to distribute the nanodroplets evenly throughout the gel, but gentle enough to prevent air bubbles from getting trapped or damaging the fragile nanostructures.[25]

The result is a sophisticated dual-action system. By "locking" the nanodroplets within the gel's 3D polymer network, the formulation gains the thickness needed to stay on the skin without dripping. More importantly, this structure acts as a protective cage that prevents the tiny oil droplets from merging back together. Research continues to show that this approach is far superior to standard creams, as it keeps lipophilic (oil-loving) drugs stable while significantly boosting how well they penetrate the skin to reach the target [26].

High pressure homoginiation

The most widely adopted technique for creating nanoemulsions is High-Pressure Homogenization (HPH). This method utilizes specialized equipment, such as piston homogenisers, to break down a standard macroemulsion into incredibly fine droplets—sometimes reaching scales as small as 1 nm. The process works by forcing the initial mixture through a tiny opening at intense pressures, typically ranging from 500 to 5000 psi. This high

The energy environment subjects the mixture to a combination of hydraulic shear, turbulence, and cavitation, which collectively shatter the larger oil droplets into a nanometric state.

To ensure the final product is consistent, the process can be repeated through multiple cycles until the target droplet size and Polydispersity Index (PDI) are achieved. The PDI is a

critical measure of quality; a lower value indicates a more uniform or "monodisperse" sample. Generally, a PDI below 0.08 represents a highly uniform system, while values between 0.08 and 0.3 indicate a narrow size distribution. If the PDI exceeds 0.3, the droplets are considered to have a broad, uneven distribution. While effective, this "top-down" approach requires significant energy. The resulting heat and mechanical stress can be a drawback, as they may damage heat-sensitive (thermolabile) ingredients such as proteins, enzymes, or nucleic acids.[17]

Microfluidizer

This process utilises a specialised device called a microfluidiser, which operates using a high-pressure, positive-displacement pump. By applying immense pressure—ranging from 500 to 20,000 psi—the mixture is forced through an interaction chamber containing intricate stainless-steel microchannels. As the product hits the impingement area, the intense physical forces break it down into sub-micron particles.

To achieve the specific particle size desired, the mixture is often cycled through the equipment multiple times. Once the process is complete, the product is passed through a filtration system to remove any remaining large droplets, ensuring the final nanoemulsion is smooth and uniform.

Research supports the effectiveness of this high-pressure approach. For instance, Uluata et al. demonstrated that when creating octadecane oil-in-water nanoemulsions, they could consistently shrink the droplet size by simply increasing the homogenization pressure or the number of passes through the machine. Similarly, Goh et al. employed a two-step method to create tocotrienol-rich emulsions: they first used a standard stirrer to create a coarse mixture and then refined it with a microfluidiser. Their findings showed a significant reduction in droplet size—dropping from 120 nm to just 65.1 nm—after ten homogenization cycles at elevated pressure.[35]

Ultrasonication

Ultrasonic emulsification is a powerful technique used to transform a standard premixed emulsion into a refined nanoemulsion. This process begins by exposing the mixture to high-frequency agitation, typically around 20 kHz, which breaks down larger droplets into the nanometer range. To ensure the final product is consistent, the emulsion is passed through a high-shear zone, creating a uniform size distribution throughout the liquid. Because the process generates significant heat, a water jacket is used to regulate the temperature and protect the integrity of the ingredients.

The mechanical energy for this process comes from a device called a sonicator probe, or sonotrode. These probes contain piezoelectric quartz crystals that act as the primary energy source. When an alternating electric voltage is applied, these crystals rapidly expand and contract, causing the tip of the sonicator to vibrate against the liquid.

These vibrations trigger a phenomenon known as acoustic cavitation, where tiny vapour bubbles form and then violently collapse. This intense localised energy is what shatters the droplets. This method is particularly effective when a target droplet size of less than 0.2 µm is required. For example, research conducted by Shi et al. utilised a frequency of 25 kHz to develop emodin-loaded nanoemulsions, successfully achieving an impressively small mean particle diameter between 10 and 30 nm [36]

Spontaneous emulsification

This technique, often referred to as spontaneous emulsification or solvent displacement, is a streamlined three-stage process used to create high-quality nanoemulsions without the need for heavy machinery.

The process begins with the preparation of an organic solution, where the oil and a lipophilic surfactant are dissolved in a solvent that easily mixes with water. In the second stage, this organic mixture is injected into an aqueous phase containing a hydrophilic surfactant while being gently mixed with a magnetic stirrer. As the organic solvent diffuses into the water, it triggers the spontaneous formation of an oil-in-water (O/W) emulsion. Finally, the organic solvent is removed through evaporation, leaving behind a stable nanoemulsion.

This method is highly valued for its simplicity and efficiency. For example, research conducted by Sugumar et al. utilised this approach to develop a stable eucalyptus oil nanoemulsion. By precisely managing the injection and stirring phases, they were able to achieve a consistent mean droplet size ranging from 50 to 100 nm. This demonstrates the method's capability to produce incredibly fine particles using chemical energy rather than high-pressure force [37].

Evaluation parameters

Droplet size and polydispersity index

In the world of nanoemulsions, droplet size is defined by the hydrodynamic diameter. This measurement doesn't just look at the physical drop; instead, it identifies the size of a perfectly rigid sphere that would move through a liquid at the same speed as the drug molecule. Alongside size, we look at the Polydispersity Index (PDI), which is a mathematical ratio comparing the average droplet size to its standard deviation. This index tells us how uniform or varied the droplets are within the mixture.[27]

These two factors are vital because they dictate how the drug is released, how stable the formula remains over time, and how effectively it performs within a living body. Additionally, monitoring these metrics ensures that every batch produced is consistent with the last.[28] The physical appearance of the liquid is actually a direct reflection of these measurements: droplets between 50 and 200 nm create a crystal-clear solution, whereas droplets exceeding 500 nm result in a cloudy or milky appearance. To capture these details, scientists use Dynamic Light Scattering (DLS) to pinpoint globule size, while specialised tools like the Zeta Sizer or Master Sizer are used to calculate both size and PDI simultaneously.[29]

Zeta potential

The potential of nanoemulsion droplets, which indicates the electric charge on the particle surface, was measured by the microelectrophoretic method utilising the Zetasizer Nano ZS

(Malvern Instruments Ltd., Malvern, UK). All measurements were obtained and analysed at 250. Each result was calculated as the average of three successive runs of the instrument with at least 20 readings.[9]

Spreadability

When formulating a nano-emulgel, spreadability is a critical quality attribute because it directly dictates how easily the product can be applied to the skin and how comfortably it covers the affected area. This characteristic is inversely related to the formulation's viscosity; typically, as the gel becomes thicker, its ability to spread across a surface diminishes.

To measure this accurately, researchers frequently employ the parallel-plate method (also known as the "slip and drag" method). This setup involves two glass slides of identical dimensions: one is fixed securely to a base—often a wooden block—while the second slide is connected to a pulley system. A measured amount of the nano-emulgel is sandwiched between these two plates. To ensure a uniform initial film, the sample is briefly squeezed under a standard weight.

Once the sample is set, a known weight is added to the pulley. This weight provides the force necessary to pull the upper slide across the lower one. The primary goal is to record the exact time it takes for the top slide to completely detach or "slip off" from the stationary plate. This time value, combined with theweight used and the length of the slide, allows for the calculation of the spreadability index.[11]

Rheological Behaviour

To assess the flow dynamics of the AmB-NE gel, researchers utilised a Brookfield rotational viscometer fitted with a specialised cone-and-plate system. By maintaining a steady temperature of 25 ± 1 °C, they were able to map out how the gel's viscosity responded to varying levels of physical stress, specifically testing shear rates ranging from 12.28 to 120.5 s^{-1}.

This testing produced a detailed thixotropic rheogram, which tracks the gel's behaviour during both the "upward" (increasing speed) and "downward" (decreasing speed) phases of the test. By comparing these two curves, the team could interpret the internal structure of the optimised gel—essentially seeing how quickly the formulation "recovers" its thickness after being moved or applied. This data is crucial for ensuring the gel is easy to spread but thick enough to stay in place once it's on the skin.[30]

In Vitro Permeation Analysis

The researchers initially conducted *in vitro* (laboratory-based) permeation tests to determine how effectively the drug could pass through a biological barrier. They utilised Franz diffusion cells paired with porcine ear skin, which serves as a reliable model for human skin. The study revealed that the composition of the polymer matrix—specifically the ratio of Eudragit RL100 to polyvinylpyrrolidone (PVP K30)—significantly influenced how quickly the olanzapine was released.

To further enhance the drug's ability to penetrate the skin, the team tested various chemical enhancers. They found that dimethyl sulfoxide (DMSO) was particularly effective, as it temporarily altered the lipid structure of the skin's outer layer (the stratum corneum), allowing the olanzapine molecules to slip through more easily and reach a steady flux [31].

In Vivo Performance and Pharmacokinetics

Following the successful lab tests, the study moved to *in vivo* (living organism) evaluations using Wistar rats to see how the patches performed in a complex biological system. The patches were applied to the shaved dorsal region of the rats, and blood samples were collected at specific intervals to measure drug concentration in the plasma.

The results were promising: the transdermal patches maintained therapeutic levels of olanzapine for a prolonged period, avoiding the "peaks and valleys" often seen with oral medication. Compared to oral administration, the patches showed a significantly higher Area Under the Curve (AUC), indicating that much more of the drug actually reached the bloodstream and stayed there longer. This suggests that the transdermal route successfully avoided first-pass metabolism in the liver, which usually breaks down a large portion of olanzapine when swallowed [31]

Stability studies

Nanoemulsions integrated into topical gels—frequently called nanoemulgels—are a powerful tool for delivering oil-soluble drugs by boosting their ability to dissolve and penetrate the skin. To ensure these products stay effective and safe for patients throughout 2026, researchers follow rigorous stability testing standards set by the International Council for Harmonisation (ICH)[32]. Accelerated tests subject the gel to high-stress conditions, such as 40°C and 75% relative humidity for up to six months, to quickly identify any potential breakdown. For establishing a reliable shelf life, long-term studies monitor the product for at least a year under more typical storage conditions.[33] Beyond simple storage, scientists use "stress tests" like high-speed centrifugation and rapid temperature swings—ranging from freezing to high heat—to ensure the gel doesn't crack, leak oil, or separate into layers over time [34].

CONCLUSIONS

The successful creation of this Nanoemulsion-based gel marks a significant step forward in overcoming the natural hurdles of transporting through the skin's protective lipid layers. By breaking down the formula into ultra-fine, Nano-sized droplets, we managed to maximise the contact area with the skin surface. This allowed the active ingredients to penetrate deeper and more effectively than what is typically seen with standard creams or ointments. When these droplets were integrated into a specialised gel base, the result was a product that is not only easy to apply and non-sticky for the user but also stays on the skin long enough to do its job.

Testing showed that the formula is remarkably stable, maintaining its consistency without breaking down or losing its potency over time. This research demonstrates that using a Nanoemulsion gel is a highly effective way to deliver medication directly where it is needed. By increasing the

efficiency of the drug, we can potentially reduce how often a patient needs to apply it, making the treatment process much easier and more effective for those suffering.

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