RESEARCH PAPER

Nanoemulsion-to-Nanoemulgel: An Advanced Strategy for Enhanced Skin Permeation and Therapeutic Efficacy

Sonam Patel [1, 2], Brijesh Singh [2], Shikha Srivastava [1*]

[1]Institute of Pharmacy, Shri Ramswaroop Memorial University, Lucknow-deva Road, Barabanki, Uttar Pradesh- 225003, India

[2] Ashoka Institute of Technology & Management (Pharmacy), Paharia, Sarnath Road, Varanasi, Uttar Pradesh-221007, India

Corresponding Author: Dr. Shikha Srivastava

Mailing address: Associate Professor Institute of Pharmacy, Shri Ramswaroop Memorial University, Deva Road, Lucknow, Barabanki, Uttar Pradesh ,225003.

Email id: shikha_ceutics@yahoo.ac.in, shikhasri.pharma@srmu.ac.in

Abstract

The topical delivery of drugs has gained much interest as a non-invasive approach for treating local as well as systemic diseases. This is mainly due to improved patient compliance, spontaneous avoidance of the first-pass metabolism as well as reduced systemic adverse effects. Conventional topical formulations, like creams, ointments, and gels, tend to have low drug permeability through the stratum corneum, ineffective skin retention, and low therapeutic efficacy. Nanoemulsions have been shown to be effective for drug delivery because of their nanosized form, high solubilizing power, large interfacial surface area and their ability to enhance the permeation of poorly water-soluble and lipophilic drugs. In spite of these benefits, their low viscosity and short residence time on the skin prevent their direct topical application. In the event of a challenge, a nanoemulsion is incorporated into the gel matrix to form a nanoemulgels that displays the high permeation properties of a nanoemulsion with the enhancement of its viscosity, stability, spreadability and patient acceptability of gels. This review presents scientific rationale for the conversion of nanoemulsions into nanoemulgels and potential of nanoemulgels for effective topical drug delivery. The formulation components, preparation, physicochemical characterization, and evaluation parameters include particle size, polydispersity index, zeta potential, viscosity, spreadability, drug content, entrapment efficiency, in vitro drug release, ex vivo skin permeation, and stability studies. The review discusses the latest therapeutic applications in dermatological disorders, wound healing, inflammatory diseases, and hyperpigmentation along with the mechanism behind enhanced skin permeation. Furthermore, recent advances regarding herbal bioactives, essential oils, QbD, multifunctional nanoemulgel systems are reviewed. In the end, ongoing challenges are examined, future perspectives discussed and opportunities for clinical translation are outlined confirming nanoemulgels a versatile and promising platform for advanced topical and transdermal delivery systems. The nanoemulgel's effectiveness for topical delivery is discussed in this piece resulting from a nanoemulsion.

Keywords: Nanoemulgel; Topical Drug Delivery; Nanoemulsion; Skin Permeation; Drug Release; Transdermal Delivery; QbD; Herbal Bioactives.

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Introduction-

The largest organ of the body acts as the first line of defence against injury by physical, chemical and microbiological agents. In addition to being a protective barrier, the skin has also become an attractive alternative route for drugs due to its non-invasive, convenient and patient-friendly approach as compared to oral and parenteral delivery systems. [1]. Topical drug delivery allows localized administration at the disease site, minimizing systemic exposure and side effects. In addition, transdermal drug delivery can also circumvent hepatic first-pass metabolism and gastrointestinal degradation and produce sustained therapeutic concentrations of the drug. Despite these benefits, the high organized structure of stratum corneum limits the effectiveness of the topical formulations as a major barrier for drug penetration.[2] As a consequence, only a few drugs penetrate the skin in therapeutically effective concentrations thus advanced novel drug delivery systems are required to enhance skin permeation while maintaining safety. Topical dosage forms such as creams, ointments, lotions, and hydrogels have been extensively used to treat skin diseases.

Nevertheless, these formulations have many drawbacks, including the poor penetration ability of drugs that are poorly water-soluble, the poor retention of drugs at the site of application, the need for frequent dosing, the instability of incorporated active pharmaceutical ingredients, and poor compliance from the patient due to an unacceptable texture or greasiness. The limitations of various drug delivery systems have led to the development of delivery systems based on nanotechnology which enhance drug solubility, stability, permeation and therapeutic performance. Nanoemulsions are an interesting nano carrier system owing to their unique physiochemical properties.[3] Nanoemulsions are colloidal dispersions that can be thermodynamically or kinetically stable systems composed of oil and water, surfactants and often a co-surfactant, the droplet of such a system is size to range 20nm-200nm. The tiny size of the droplets increased the surface area of the interface, solubilized the drug, contacted the skin surface, and improved the transport of drug molecules to the stratum corneum. Moreover, the surfactants and the co-surfactants present in nanocarriers temporarily change lipid arrangement of the skin barrier, improving drug permeation. Due to above-mentioned properties, they are suitable carriers for lipophilic drugs, phytoconstituents, antioxidants and poorly soluble drugs. Despite significantly enhancing drug permeation, the nanoemulsion alone does not serve as an ideal topical dosage form. [4] The low viscosity of these materials means they are prone to leakage, becoming disseminated beyond the area of application and removed from the skin surface quickly due to movement, sweat, or unintended contact. So, this reduces the residence time of the formulation on skin and consequently drug absorption and efficacy. [5] Moreover, the handling and dosing of liquid nanoemulsions may be inconvenient to the patients which may reduce their acceptability. Nanoemulsion are incorporated into suitable gel matrices to produce nanoemulgel to overcome these limitations. A nanoemulgel offers both the drug-loading capacity and penetration-enhancing properties of nanoemulsion and the favourable rheological properties of hydrogels. The addition of gelling agents to liquid nanoemulsion can produce a semisolid dosage form without compromising the nanoscale droplet characteristics of the emulsion. Some commonly used gelling agents include Carbopol, hydroxypropyl methylcellulose (HPMC), xanthan gum, sodium carboxymethyl cellulose, poloxamers, and similar additives.[6] By converting the nanoemulsions into semi-solid dosage forms, viscosity is improved which increases skin residence time, offers controlled drug release, reduces run-off of formulations and enhances ease of use without losing the permeation advantages of nanoemulsion systems. The improved therapeutic performance of nanoemulgels is due to the contribution of both formulation components. The nanoemulsion enhances drug solubility, improving skin partitioning for better permeation. While, Gel matrix prolongs contact with application site for sustained drug release. Consequently, nanoemulgels have shown significant potential for topical management of inflammatory diseases, bacterial and fungal infections, acne vulgaris, psoriasis, wound healing, osteoarthritis, skin cancer, hyperpigmentation diseases and other dermatological diseases.[7] Most Recently, researchers studying nanoemulgels containing herbal extracts, essential oils, antioxidants, and other natural bioactive molecules are gaining increasing interest, as this can offer a synergic effect of better delivery and organics. In recent times, advancements in pharmaceutical nanotechnology opened the floodgates of nanoemulgel study. The use of quality-by-design (QbD) principles, systematic optimization of formulation variables, advanced characterization techniques, as well as in vitro, ex vivo and in vivo evaluation are modern formulation approaches to enhance product quality and reproducibility. Moreover, the development of multifunctional nanocarriers, stimulus-responsive systems, and computing formulation optimization will further increase the clinical potential of nanoemulgels.[8] The commercialization of the technology is still subject to important hurdles like long-term physical stability, large-scale manufacturing, regulatory approval, reproducibility and clinical translation. Thus, a thorough understanding of the scientific rationale behind the nanoemulsion to nanoemulgels conversion is need of the hour for the scientists involved in topical and transdermal drug delivery. The objective of the review is to critically summarize what is known nanoemulgel technology in terms of formulation design and preparation methods, physicochemical characterization, mechanism of enhanced skin permeation, biological evaluation, therapeutic application, recent technological advances and future scope for research. Through the integration of findings obtained from published studies, this review provides an up-to-date overview of nanoemulgel-based drug delivery systems.[9] In addition, the focus on the technological advancement highlights the increasing relevance of nanoemulgels systems which has emerged as a high potential technique for enhancing therapeutic efficacy during topical application.

2. Skin Anatomy and Drug Permeation

2.1 Skin Anatomy

The skin is the largest organ of the body. It weighs around 15-16% of total body weight and covers an area of nearly 1.5-2.0 m² in adults. As the first line of defense, the skin protects the body from excessive loss of water.[10] Moreover, it also offers a shield against mechanical injury, UV rays, microbes, and harmful chemicals. The skin not only acts as a barrier but also helps to regulate the body temperature, partakes in immune responses, senses, and helps make vitamin D. The skin due to its large surface area and easy accessibility has become an attractive route for topical and transdermal drug delivery.[11] The skin is composed of three main structural layers, namely the epidermis, dermis, and hypodermis (subcutaneous tissue). Each layer possesses unique anatomical and physiological characteristics that affect drug permeation and efficacy.

2.1.1 Epidermis

The epidermis is the outermost layer of skin and serves as the main protective barrier. It is a multi-layered squamous epithelium which is not supplied with blood vessels. Its thickness is between 50 to 150 µm depending on the part of the body where it is located. The epidermis makes up a skin's outermost layer. It contains many cells, nearly all keratinocytes. The epidermis is made up of 5 layers.[12] Stratum corneum; Stratum lucidum (present only in thick skin like palms and soles); Stratum granulosum; Stratum spinosum; Stratum basale (germinativum). Stratum corneum is a major barrier to drug penetration. It consists of flattened cells (corneocytes) that are dead and held together with keratin that are embedded in a lipids matrix. This physical organization substantially hampers the penetration of most therapeutic molecules through the skin.

2.1.2 Dermis

The dermis is thicker than the epidermis (1–4 mm). It lies beneath the epidermis. It is made up of mainly collagen and elastin fiber within the extracellular matrix rich in glycosaminoglycans. The dermis is responsible for the strength, elasticity and support of the skin.[13] Found in this layer, you'll find blood vessels, lymphatics, hair follicles, sebaceous glands, sweat glands, nerve endings and immune cells. Once a drug crosses the skin surface, it diffuses through the dermis and may enter the dermal capillary network. This local or systemic effect depends on the formulation and indications.

2.1.3. Hypodermis (Subcutaneous Tissue). The hypodermis or subcutaneous layer is the deepest-layer of the skin containing adipose tissue. [14]and connective tissue. The hypodermis is not considered an actual skin layer. It achieves various physiological purposes. For example, it cushions, energy storage, insulation against temperature fluctuation, and attachment to muscles and bones. It is the last tissue drug of transdermal delivery. After reaching here, the drugs enter the vascular network of the skin and reach circulation. [15]

2.1.4 Skin Barrier Function

The outermost layer of skin is the primary barrier to drug delivery. The arrangement of highly ordered lipid bilayers that block entry of hydrophilic molecules and high-molecular-weight substances. In general, skin permeation may be better for molecules with a molecular weight below 500 Da, moderate lipophilicity, and adequate aqueous solubility.[16] Nanocarrier-based drug formulations, especially nanoemulgels, promote drug transport through various mechanisms. Firstly, they increase drug solubility. Secondly, they enhance skin surface contact. Thirdly, they modify lipid organization of the stratum corneum. And finally, they prolong residence time at the application site. These factors lead to the skin permeability of drugs. Skin penetration of topically applied drugs occurs by means of 3 pathways

2.2 Pathways of Drug Permeation Through the Skin

Topically applied drugs can penetrate the skin through three principal pathways**:**

2.2.1. **Intercellular Pathway-** The transcellular, or intracellular, pathway involves the drug molecules moving through the stratum corneum corneocytes.[17] Since the drug is forced to cross these alternating hydrophilic and lipophilic domains repetitively, this route is generally suitable for small molecules with balanced physicochemical properties.

2.2.2. The intercellular pathway is the main route of administration used for drugs. The lipid matrix between corneocytes allows for drug diffusion. Formulations of nanoemulsion enhance this pathway by disturbing or fluidizing the lipid bilayer via surfactant and co-surfactant to improve skin permeation.

2.2.3. **Transappendageal (Follicular) Pathway** -The transappendageal (follicular) way involves the skin appendages as the route for drug transport. The skin appendages are the hair follicles, sebaceous glands and sweat glands.[18] Besides, these structures only occupy a small area in the overall skin surface yet they are an important route for nanoparticles and useful in targeted follicular drug delivery.

3. Relevance of Skin Anatomy to Nanoemulgel-Based Drug Delivery

Importance of Skin Structure for Nanoemulgel-Based Drug Delivery. Nanoemulgel efficacy is related to skin anatomy. Nano-sized droplets create a large surface area for interaction with skin and surfactants enhance the partitioning of drugs into the lipid-rich stratum corneum. When a nanoemulsion is incorporated into a gel, its viscosity increases and the contact time with the skin surface is prolonged, leading to enhanced permeation, [19] sustained drug release and therapeutic action. Because of these various properties, the nanoemulgels could be used in the treatment of several dermatological disorders such as acne, psoriasis, fungal infections, etc. As depicted in figure 1, the drug permeation pathways of skin anatomy with relevance to nanoemulgel-based transdermal delivery.

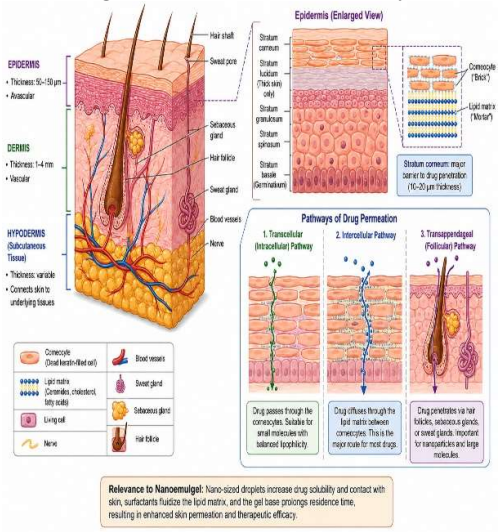

Figure.1. Skin anatomy and pathway of drug permeation

4.Nanoemulsion

4.1. Definition of Nanoemulsion

Nanoemulsions are sophisticated colloidal systems used for drug delivery comprising of two immiscible liquids (oil and water) which are stabilized by surfactants and frequently, by co-surfactants too. Their droplet sizes usually fall between 20 and 200 nm, giving them a transparent or translucent appearance and an excellent kinetic stability.[20] Nanoemulsions have the potential to increase the solubility, dissolution rate, bioavailability, and skin permeation of poorly water-soluble drugs due to their nanoscale size and increased interfacial surface area. They have emerged as effective carriers for many drug delivery approaches including topical transdermal and oral. Due to their ability to enhance skin surface drug distribution, prolong drug retention, and promote stratum corneum penetration, nanoemulsions are highly beneficial for topical drug delivery. But due to their low viscosity and poor residence time on skin, they are commonly incorporated into gel matrices to form nanoemulgels. [21] The nanoemulsion consists of oil droplets, an aqueous phase, and an emulsifier interface as illustrated in figure 2.

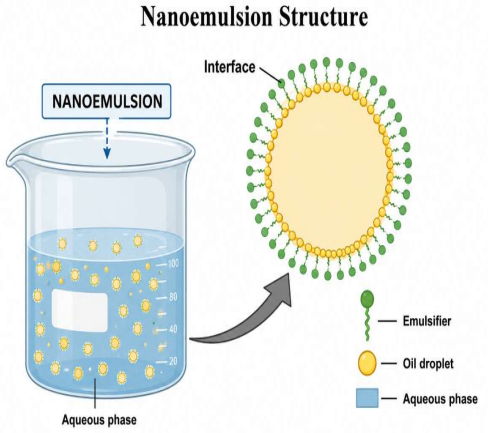

Figure.2. Structure of Nanoemulsion

4.2. Classification of Nanoemulsions

Nanoemulsions, which are two immiscible liquid colloidal dispersions, normally aqueous and oily, are stabilized by surfactants and co-surfactants. Depending upon the dispersed and continuous phases, nanoemulsions can be broadly classified into Oil-in-Water (O/W), Water-in-Oil (W/O) and bicontinuous nanoemulsions.[22] Each type has unique physicochemical properties that affect drug loading, stability and therapeutic uses.

4.3. Water-in-oil emulsions. **Oil-in-water (O/W)** nanoemulsions are nanosized oil droplets uniformly distributed in the aqueous phase. Nanoemulsions with Droplet Sizes > 200 nm are the type of nanoemulsion that is mostly used for pharmaceutical and cosmetic application as they are non-greasy, easily spreadable, and can be easily removed from the skin. O/W nanoemulsions are ideal for the delivery of lipophilic drugs as the oil phase is dissolved with the drug, while the external aqueous phase confers a pleasant sensory feel.[23] The small size of the droplets increases the solubilization of the drug, improves the permeability into the skin and increases its bioavailability. These systems find applications in topical creams, lotions, nanoemulgels, oral formulations, and cosmetic products.

4.4. Nanoemulsion of Water-in-Oil Water-in-oil nanoemulsions are oil-continuous emulsions that consist of aqueous droplets. These creams have a higher oil level compared to lotions, making them more moisturizing, occlusive.[24] Without nanoemulsions, the skin's transepidermal water loss causes prolonged hydration. Hydrophilic drugs are commonly

delivered from them, as well as products for dry skin conditions.

4.5. Bicontinuous Nenuemulsion Bicontinuous nanoemulsions are made with a continuous network of oil and water phases where oil is not completely dissolved in water and vice versa. This unique design has a high interfacial area which enhances drug solubility of hydrophilic as well as lipophilic drugs. Bicontinuous nanoemulsions can be formed only under specific formulation condition and require [25]careful optimisation of surfactant to oil ratio. Although more complex in structure, they are not as commonly used as O/W and W/O nanoemulsions but have potential for advanced drug delivery systems. The component of nanoemulsion is showing below table 1.

Table 1. *Different components of nanoemulsion*

Component	Function	Examples
Oil Phase	Solubilizes lipophilic drugs and influences droplet size	Isopropyl myristate, Olive oil, Coconut oil, Castor oil, Medium-chain triglycerides
Surfactant	Reduces interfacial tension and stabilizes droplets	Tween 20, Tween 80, Span 20, Span 80
Co-surfactant	Further reduces interfacial tension and improves flexibility of the interfacial film	PEG 400, Propylene glycol, Ethanol, Transcutol® P
Aqueous Phase	Continuous phase in O/W nanoemulsions	Distilled water, Purified water, Phosphate buffer

5.Methods of Preparation

Ways to Prepare A nanoemulsion is made of water and oil that are immiscible liquid blended with a surfactant and co-surfactant to make droplets of the nano-range (20–200 nm). The coating method selection is done by the physicochemical characteristics of the drug,[26] size of droplets desired, composition of formulation and stability of formulation, scaling up, and route of administration. Preparation methods of nanoemulsion are broadly classified into high-energy methods and low energy methods based on the energy requirement for emulsification.

5.1 High-Energy Emulsification Methods

High-Energy Emulsification Processes High-energy methods employ mechanical means to create intense disruptive forces that reduce droplet sizes to the nanometer range. [27]The pharmaceutical industry uses these techniques of these[28] because they provide nanoemulsions with good droplet size distribution and physical stability.

5.2. High-Pressure Homogenization (HPH)

High-pressure Homogenization (HPH). High-pressure homogenization is a widely used method for the preparation of nanoemulsions. A coarse emulsion is forced through a narrow homogenization gap under high pressures in this technique (usually 500-1500 bar). Using cavitation, turbulence, and shear stress for breaking up large droplets into nanosized droplets to obtain a stable nanoemulsion with a narrow nanoemulsion droplet size distribution.[29] This method can be easily reproduced on an industrial scale.

5.3. Ultrasonication

Ultra sonicating Ultrasonication implements high-frequency ultrasonic waves that create bubbles in the emulsion (20–100 kHz). As these bubbles burst, they create localized shear forces that help reduce the size of the droplets. [30] Ultrasonication is easy, fast, and ideally suited to laboratory scale formulation development. Nanoemulsions are often used to enhance homogeneity and stability.

5.4. Microfluidization

Microfluidization is pumping a coarse emulsion through microchannels at high pressure with opposing fluid streams colliding at high speed. This process produces very fine and uniformly dispersed droplets. It leads to nanoemulsions which are extremely physically stable and reproducible.

5.5. Low-Energy Emulsification Methods

Low energy emulsification techniques Low-energy approaches depend on formulations' physicochemical properties and not on the mechanical forces.[31] These techniques consume less energy and are beneficial for thermolabile drugs.

5.6.Phase Inversion Temperature (PIT) Method- The PIT approach relies on varied temperature-induced changes in the affinity of nonionic surfactants for oil and water. At the phase inversion temperature, the interfacial tension is so low that nanosized droplets start to form upon cooling.

5.7. Phase Inversion Composition (PIC) Method. The PIC method involves changing the composition of the system in a gradual manner to develop nanoemulsions. Generally, an aqueous phase is gradually added to an oil–surfactant mixture. [32] Change in composition causes phase inversion and produces fine droplets without requiring excessive mechanical energy.

5.8. Spontaneous Emulsification

Spontaneous emulsification is a self-emulsifying technique that occurs when the oil phase comprising surfactant and co-surfactant are added under gentle stirring into the aq phase. Because of the rapid dispersion of the co-surfactant and the drop in interfacial tension, nanosized droplets spontaneously form. This procedure is straightforward, low-cost and applicable to heat-sensitive materials.

5.9 Mechanism Nanoemulsion

Nanoemulsions improve drug delivery by several means.

• Enhance drug solubility.

• Enhance the speed of disintegration.

• Make absorption possible through increased surface area.

• Improve the moisture level of the skin.

• Disrupting the stratum corneum's lipid packing.

• Enhance drug distribution within the skin.

• Enable the tight control and prolonged release of drugs.

a. Rise in Drug Solubility. Nanoemulsions can be utilized to enhance the solubility of drugs or phytoconstituents that are poorly soluble in water when the poorly soluble material is included in the internal oil phase or at the oil-water interface. Many bioactive plant constituents that are present in herbal extracts are poorly soluble in water. Therefore, the incorporation into the oil phase of a nanoemulsion can maintain the constituents in a solubilized state. [33] In your formulation, an appropriate choice of the oil phase, surfactant and co-surfactant can enhance the solubilization of active constituents from the leaf extract of Nyctanthus arbor-tristis. This may help to keep the active substances in a suitable dispersed form, and may improve their availability at the skin surface.

b. Dissolution Rate is Found to Improve. Minimizing each one of the dispersed droplets provides an addition of the interfacial area between the formulation and surrounding aqueous phase. The fast transfer of solubilized constituents utilized in the formulation offers advantages for dispersion. The tiny drop size of a nanoemulsion therefore has a rapid dissolution/release behaviour as compared to a conventional coarse emulsion, especially for poorly aqueous soluble constituents.

c. Increase in Surface Area for Absorption

A defining characteristic of a nanoemulsion is small droplet size, which is usually measured in nano range. Through the decrease in droplet size, the total surface area available for agglomeration with the surrounding medium and skin increases. The enlarged interfacial area promotes close interaction between the formulation and skin surface. This might improve the movement of integrated phytoconstituents into and toward skin. In a topical nanoemulgel, the nanoemulsion droplets are evenly distributed throughout the gel matrix, thereby increasing the effective surface area of the formulation on application.

d. Enhancement of Skin Hydration

Topical nanoemulsions could modulate the hydration of the stratum corneum. The formulation can help prevent water loss from the skin and increase the presence of water at the skin surface level. Increased moisture in the skin causes swelling and movement of cells in the skin. Because of this, the barrier properties of the stratum corneum may be changed on a short-term basis, facilitating penetration of the active constituents incorporated. [34] The mechanism is especially important for topical formulations, as hydrated skin enables greater diffusion of many substances as compared to being overly dry and compact.

e. Disruption or fluidization of stratum corneum lipid packing can occur in the treatment of a skin condition. The skin's outermost layer, or stratum corneum, impedes the penetration of any topical drug. It has a very specific lipid organization comprising mainly ceramides, cholesterol and fatty acids. Surfactants, as well as co-surfactants, present in nanoemulsions can get in contact with the intercellular lipids and lead to a temporary increment in lipid fluidity or a decrease in the ordering of packing of the barrier.[35] Through the stratum corneum, diffusion of the incorporated active constituents can be enhanced by modifying the environment. Nonetheless, the type and concentration of the surfactant/co-surfactant strongly influence lipid disruption.

Excessive disruption of skin may cause irritation hence optimum formulation.

f. Enhancement in the Partitioning of the Drug to the Skin. For a formulation to be able to penetrate the skin, it must be able to partition from the formulation itself into the stratum corneum. Nanoemulsions can enhance this process on account of the huge interfacial contact area they provide and due to the modification of the thermodynamic and physicochemical environment of the incorporated compound. The partition coefficient of the active constituent between formulation and skin may be influenced by oil, surfactant, and co-surfactant. Therefore, the nanoemulsion can help facilitate the migration of phytoconstituents [36] from the formulations to the lipophilic structures of the SC and then into deeper skin layers.

6. Controlled and Sustained Drug Release

When a nanoemulsion is integrated into a gel matrix to manufacture a nanoemulgel, it is probable that the gel network enhances formulation viscosity and slows down the movement of droplets and solutes. It allows the formulation to stay in contact with the application site for a prolonged period while also minimizing rapid runoff or removal from the skin surface. Thus, drug or phytoconstituent release may become relatively more controlled and sustained than a simple low-viscosity formulation. The real performance in release, nonetheless, depends on the composition and structure of the nanoemulsion and gel system and should be verified experimentally through a suitable in-vitro release study. The flowchart provides a brief overview of the mechanism.

Nano-sized droplets
↓
Increased solubilization + increased surface area
↓
Close contact with skin surface
↓
Improved hydration of stratum corneum
↓
Modification/fluidization of intercellular lipid structure
↓
Enhanced partitioning of phytoconstituents into skin
↓
Improved penetration and retention in target skin layers
↓
Prolonged residence due to nanoemulgel matrix
↓
Potentially improved topical delivery of *Nyctanthus arbor-tristis* phytoconstituents

7.Conversion of Nanoemulsion into Nanoemulgel

It is reported that nanoemulsions exhibit great potential in improving solubility, stability and skin permeation of therapeutic agents. However, application directly on skin is limited due to their low viscosity and liquid nature.[37] These features generally lead to poor retention at the site of application, leakage during use, difficulty in dosing, and reduced contact time with the skin compromising efficacy. In order to overcome these restrictions, a nanoemulsion is incorporated into a suitable gel matrix to make nanoemulgels, an amalgamation of a drug delivery system that benefits from nanoemulsions and hydrogels.[38] The nanosized droplets responsible for improved drug permeation in nanoemulgels are retained while the other beneficial properties such as increased viscosity, better spreadability, prolonged skin retention time, good ease of application and better patient acceptability of gels are acquired. As a result, nanoemulgels have emerged as a very promising topical drug delivery system for the management of skin diseases.

Table 2: Components involved in the conversion of nanoemulsion into nanoemulgel and their functional roles

Nanoemulsion Component	Conversion Step	Nanoemulgel Function
Oil phase	Retained within nanoemulsion droplets	Solubilization of lipophilic constituents
Surfactant/co-surfactant	Stabilize nanoemulsion droplets	Support interfacial stability and skin interaction
Aqueous phase	Continuous phase of nanoemulsion	Provides dispersion medium
Gelling polymer	Added to nanoemulsion system	Provides semisolid consistency

		and viscosity
Nanoemulsion	Incorporated into gel base	Provides nanosized droplets within gel matrix
Final nanoemulgel	Homogenized semisolid formulation	Prolonged contact with skin and improved handling

Principle of Formation Nanoemulgels. [39] The nanoemulgel formulation disperses a preformulated nanoemulsion into a gel base containing the appropriate excipients under continuous stirring. As a result of this process, the nano-sized droplets are uniformly dispersed in the three-dimensional polymeric gel network without the alteration of the size and stability of the particles. The matrix of the gel serves as a barrier to diffusion and thus releases the drug gradually, while keeping the formulation in close contact with the skin surface.

8.Advantages of Nanoemulgel over Nanoemulsion.

Parameter	Nanoemulsion	Nanoemulgel
Physical state	Liquid	Semisolid
Viscosity	Low	High
Skin retention	Poor	Excellent
Residence time	Short	Long
Drug release	Rapid	Controlled and sustained
Leakage	High	Minimal
Spreadability	Moderate	Excellent
Patient compliance	Moderate	High
Ease of application	Moderate	Excellent
Therapeutic efficacy	Good	Improved

9. Recent Advances in Nanoemulgel Technology

Recent developments in nanotechnology and pharmaceutical sciences provide enhanced design, performance and clinical potential of the nanoemulgels.[40] The recent nanoemulgel formulations are not only made to enhance drug solubility and skin permeation but also provide targeted delivery, sustained drug release, stabilisation, better patient compliance and multi-functionality. The incorporation of new polymers, biocompatible natural compounds and smart materials has vastly extended the applications of nanoemulgels in dermatologic, wound healing and transdermal applications, as well as cosmetics. [41]

10. Herbal and phytochemical based nanoemulgels

Bioactive compounds possess properties that are antioxidant, anti-inflammatory, antimicrobial, and wound healing. Many phytoconstituents, [42] on the other hand, have poor solubility, and skin penetration. Using nanoemulgel technology, it can overcome these limitations.

11. Therapeutic Applications of Nanoemulgels

Nanoemulgels are a new dosage form which has been used for topical drug delivery. Nanoemulsions are known for their superior drug solubilization and skin permeation while hydrogels are viscous in [43] nature and more patient friendly. The bioavailability of a poorly water-soluble drug is improved considerably by this hybrid system. Moreover, it extends the skin residence time and provides controlled release of drug from the system which is beneficial for the treatment of several dermal and systemic maladies. [44] In dermatology, particularly for acne vulgaris, psoriasis, eczema, atopic dermatitis, and rosacea, nanoemulgels are highly studied as they improve drug penetration into deeper skin levels while minimizing systemic side effects. There is considerable evidence of their potential in the treatment of hyperpigmentation disorders including melasma, related to the improved topical delivery of depigmenting agents such as kojic acid, arbutin, tranexamic acid, niacinamide and herbal phytoconstituents. Also, [45] the localized application of nanoemulgels for antifungal and antibacterial therapy helps treat skin infections while minimizing application frequency. As a result of the results of the platform upon application in wound healing whereby nanoemulgels incorporating herbal extracts along with other compounds antioxidants or anti-microbial were prepared to accelerate tissue

regeneration with reduced microbial contamination. Moreover, they are becoming more common for delivering anti-inflammatory and analgesic drugs topically in the case of osteoarthritis and musculoskeletal disorders. They offer lasting efficacy along with better compliance. The aesthetic appeal and spreadability of nanoemulgels make them suitable in cosmeceuticals including anti-aging, whitening, moisturizing, and sunscreen formulation. [46] As advancements in nanotechnology and formulation techniques continue to be made, nanoemulgels have shown to have a growing therapeutic window, thus representing an versatile and effective modern topical and transdermal drug delivery platform.

12.Future Perspectives of Nanoemulgel

The future of topical and transdermal drug delivery will be greatly influenced by nanoemulgel technology, which overcomes the limitations of conventional formulations. Studies are being conducted for the development of multifunctional nanoemulgels for targeted drug delivery, controlled release, [47] enhanced skin permeation and improved therapeutic efficacy. The use of natural bioactive compounds, herbal extracts, essential oils, and phytochemicals in nanoemulgel.

systems has now attracted significant attention due to their safety, biocompatibility, and wide-range pharmacological activities. Research in the future will likely focus on Quality by Design (QbD) approach, Artificial intelligence (AI) assisted formulation development to optimize formulation variables, predict stability, and reduce development time. [48] The use of stimuli-responsive (smart) nanoemulgels capable of releasing drugs in response to changes in pH, temperature, enzymes or light, presents novel opportunities for personalized and targeted therapy. Nanotechnology can facilitate the development of nanoemulgels with enhanced drug loading and stability as well as superior retention in the skin. [49] The combination of 3D skin models, advanced imaging, and computational modeling will improve our understanding of permeation mechanisms and speed up preclinical evaluation. Also, large-scale production, regulatory standardisation and large-scale clinical testing are needed to assure the product quality, safety and efficacy as well as commercial success. It is expected that nanoemulgels in the future will have uses in transdermal delivery of peptides, vaccines, biologics, and gene-based therapeutics apart from dermatological ailments. In all, the ongoing developments in formulation scientist [50] and biomaterials and also pharmaceutical nanotechnology will make the nanoemulgel an emerging new generation platform for a safe, effective and patient-compliant drug delivery system with wide use in the pharmaceutical and cosmeceutical industries.

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