

REVIEW ARTICLE**Nanoemulgel as an Advanced Topical Drug Delivery System:
Formulation, Characterization, and Applications****Tanuja Sharad Gunjal**

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Email: tanugunjal02@gmail.com**ABSTRACT**

Nanoemulgel, a novel hybrid drug delivery system based on Nanoemulsion and Gel technology, has proven to be a breakthrough in the field of Topical and Transdermal Drug Delivery. Traditional topical products (creams, ointments and plain gels) do not penetrate the stratum corneum (SC), the main barrier of the epidermis, to the target site sufficient enough to reach therapeutic levels of drug at the target site. The latter are overcome by Nanoemulgel which combines the drug solubilization and penetration-enhancing properties of nanoemulsions with the sustained release and enhanced patient compliance of gel-based systems. This review provides a thorough overview of the concept, formulation approaches and physicochemical properties of nanoemulgel systems. The structure of skin and its barrier function is explained with reference to the barrier penetrating ability of the nanoemulgels involving transcellular, intercellular and appendageal pathway. High energy and low energy fabrication techniques are described, as well as optimization techniques such as Quality by Design (QbD), critical characterization parameters including droplet size, zeta potential, in vitro drug release and ex vivo permeation. Nanoemulgels have a broad range of therapeutic uses such as anti-inflammatory, antifungal, antibacterial, anticancer, antiacne, anti-psoriatic, herbals and cosmetics. Emphasis is placed on recent developments such as stimuli-responsive systems, 3D printed patches and self-nanoemulsifying gel systems. The review also covers the issues of scale-up, regulatory compliance and stability concerns. In summary, nanoemulgel is a scientifically promising and clinically relevant platform that needs to be explored for further translations and standardized regulatory processes towards commercialization. Nanoemulgel (nanoemulsion) Topical Drug Delivery System (nanoemulgel) Nanoemulsion Skin Permeation Transdermal Drug Delivery.

Keywords: Nanoemulgel; Nanoemulsion; Topical Drug Delivery; Transdermal Drug Delivery; Skin Permeation; Stratum Corneum; Drug Release; Penetration Enhancement; Nanotechnology; Quality by Design (QbD).

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INTRODUCTION

The skin is the largest organ in the human body, covering about 1.8 m² of body surface and is a major interface between the internal and external environment. Such a unique anatomical situation has, for many years, rendered skin an appealing vehicle for drug delivery, not only for local dermatologic treatments, but also for systemic therapeutic effects via transdermal absorption. Topical drug delivery systems (TDDS) have some very promising advantages over the traditional oral and parenteral routes of drug delivery, including: Avoidance of first pass hepatic metabolism, reduction in gastrointestinal side effects, controlled drug release, improved patient compliance and ease of application and termination of therapy [1, 2]. However, the barrier properties of skin, especially the outermost layer (stratum corneum), have long posed difficulties to formulation scientists in developing effective topical agents. The stratum corneum consists of corneocytes, which are flattened, protein-rich cells surrounded by an extracellular matrix that is lipid-rich, and prevents the permeation of most drug molecules, particularly those that are hydrophilic, of high molecular weight and/or poor skin lipid solubility. Topical conventional dosage forms such as creams, ointments, lotions and plain gels are common and are widely used to prescribe drugs but they often do not provide adequate therapeutic levels of a drug at the target tissue [3, 4]. Although creams and ointments are good occlusive agents, they are not well accepted by the patient, have a greasy consistency, and do not allow precise control of drug release [5]. Conventional gels have good aesthetic

properties, but suffer the drawbacks of being incapable of incorporating hydrophobic drugs and of being poor penetration enhancers. Such limitations have spurred pharmaceutical scientists to seek more sophisticated nanotechnology platforms that are capable of effectively crossing the skin barrier without sacrificing elegance and stability of the formulation [6]. Nanoemulgel is one of the innovative approaches developed over the last 2 decades being a promising hybrid drug delivery system. A nanoemulgel is a nanoemulsion (i.e., an optically isotropic, thermodynamically or kinetically stable dispersion of oil in water or of water in oil having droplet size range of 20–500 nm) which is dispersed in an appropriate gel matrix [7, 8]. The solubilisation ability and permeation enhancing property of the nanoemulsion is combined with high viscosity, prolonged contact time and ease of application of the gel base. The idea of “nanoemulgel” has rapidly broadened and forms are currently available for various classes of drugs, such as NSAIDs, antifungals, antibacterials, anticancer agents, herbal extracts and cosmeceuticals. The formulation science and nanotechnology developments have resulted in the formulation of stimuli responsive, biodegradable and patient specific nanoemulgel systems with tremendous potential both in dermatological and systemic therapeutic arena [9, 10]. The objective of this review is to give an all-encompassing, up-to-date and critically reviewed account of nanoemulgel, as an advanced topical drug delivery system. It includes the basic concepts and composition, structure of skin and implications for drug delivery, formulation and optimization techniques, characterization technique, various therapeutic applications, recent advances in techniques, current challenges, regulatory aspects and future directions of nanoemulgel research.

What is Nanoemulgel?

Nanoemulgel: A semi-solid dosage form comprising of a nanoemulsion dispersed in a hydrophilic or hydrophobic gel base. It offers the best of both nanotechnology and gels in terms of physicochemical properties and produces a formulation that offers better drug delivery efficiency, stability, and patient acceptability. The 'nano' part of the term 'nanoemulgel' describes the very small size of the droplets of the dispersed phase, the 'emul' part, from emulsion, and the 'gel' part, denoting a semisolid matrix [11, 12]. It is important to differentiate nanoemulgel from other related systems. In a conventional emulgel, the emulgelled droplets are larger than 1 μm , and are gelled with a polymer, while a nanoemulgel comprises of a nanoemulsion (droplet size 20–500 nm) within a gelled matrix [13]. Nanoemulgel has significantly smaller droplet size that provides high stability, high surface area for drug absorption, high permeability of membranes and high drug bioavailability compared to emulgels. Another, and particularly important, distinction to be made is between nanoemulgel and microemulgels, which are thermodynamically stable microemulsions (droplet size 10 - 100 nm), which require a higher concentration of surfactant [14]. Nanoemulgels possess a number of interesting physicochemical properties, such as their optical clarity or near-transparency, low viscosity of the internal nanoemulsion phase and gel-like external rheology, which makes them especially attractive for topical application [15]. The nanodroplets improve the partitioning of drugs in the stratum corneum and the gel matrix leads to a slow release of the drug and ensures a long-term contact with the skin.

COMPONENTS OF NANOEMULGEL

Oil Phase

An important part of the nanoemulsion core of nanoemulgel is the oil phase. It is mainly influenced by the solubility of the drug, in that the oil should be able to encapsulate as much drug as possible. The oils that are most commonly used are medium-chain triglycerides (MCT) including Miglyol 812, oleic acid, isopropyl myristate, isopropyl palmitate, castor oil, soybean oil, and eucalyptus oil [16]. Selection of oil also helps in determining the droplet size, stability and in vitro release rate of the formulation. A preferred surfactant system is one for which the oils have low interfacial tension when mixed with the system [17].

Aqueous Phase

In the most common of the types formed for topical application, the continuous phase is in the form of purified water, and it is this that forms the aqueous phase in the oil-in-water (O/W) type of nanoemulsion. Buffer solutions can be added to keep the pH within the human physiology range of 4.5–6.5, which is close to the pH of the skin and therefore less irritating to the skin. Water-soluble additives like humectants and preservatives could also be present in the aqueous phase [18, 19].

Surfactants and Co-surfactants

Amphiphilic molecules, known as surfactants, lower the interfacial tension at the oil-water interface, and thus promote the formation and stabilization of nanodroplets. Their selection is based on the Hydrophilic-Lipophilic Balance (HLB) value, where O/W nanoemulsions are a case in point, and use a surfactant having an HLB value of 8-18 [20]. Non-ionic surfactants have less potential for skin irritation

than ionic surfactants, and are preferred for topical applications. Common surfactants used are Tween 20, Tween 80, Span 20, Cremophor EL, Labrasol and Kolliphor RH40. To achieve a stable formation of nanoemulsion, co-surfactants like Transcutol P, polyethylene glycol (PEG) 400 and propylene glycol are added to further decrease the interfacial tension, increase drug solubility and increase the fluidity of the interfacial film [21].

Gelling Agents

Gelling agents convert the liquid nanoemulsion to a semi-solid dosage form which can be applied topically. The choice of gelling agent is related to their compatibility with the components of the nanoemulsion, mechanism of gelation, desired rheological properties and tolerability to the skin. The most commonly used synthetic gelling agents are the polymers that are known as carbopol or carbomer and which are able to form very viscous gels when neutralized with triethanolamine or sodium hydroxide [22]. Cellulose based gelling agents such as Hydroxyethylcellulose (HEC), Hydroxypropyl methylcellulose (HPMC), and Sodium carboxymethylcellulose (Na-CMC) are widely used in the formulation of nanoemulgel. The natural polymers (xanthan gum, guar gum and chitosan) also have the advantage of being biodegradable and biocompatible. The amount of gelling agent should be optimized to give sufficient viscosity but not reduce drug release or spreadability [23, 24].

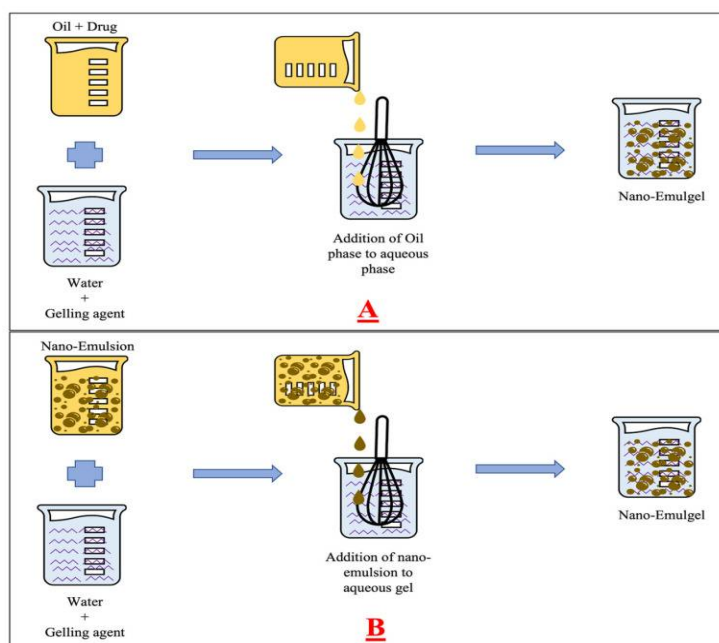


Figure 1: Structure and Components of Nanoemulgel

Penetration Enhancers

Chemical penetration enhancers are added to aid in drug penetration through the S.C. They temporarily and reversibly disrupt the barrier properties of the S.C. They work by disrupting the intercellular lipid bilayers, changing its solubility and partitioning in the skin, or by binding to the protein in the corneocytes. Nanoemulgel formulations are based on common penetration enhancers, including oleic acid, propylene glycol, dimethyl sulfoxide (DMSO), Azone (1-dodecylazacycloheptan-2-one), and other terpenes like menthol and eucalyptol [25, 26].

Preservatives, Antioxidants and Humectants

Anti-microbial preservatives like methylparaben, propylparaben and benzalkonium chloride are added to protect the aqueous phase from microbial contamination. Antioxidants like butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) and tocopherol are used to prevent oxidative degradation of labile drug molecules or lipid molecules. The ingredients of the formulation, like humectants with the name glycerin, sorbitol or propylene glycol, help to preserve a level of skin hydration and enhance the moisturizing effect [27, 28]. The properties of an ideal nanoemulgel. The desirable characteristics of an ideal nanoemulgel are droplet size less than 200 nm and PDI less than 0.3, which indicates a narrow size distribution and monodispersity; zeta potential of ± 30 mV or above, which is essential for ensuring electrostatic stability; pH in the range of 5.0–7.0 for skin compatibility; adequate viscosity (typically 1000–50,000 mPa·s) to allow the easy spreading onto the skin and allowing prolonged skin contact; and

excellent drug entrapment efficiency (>80%). Further, the formulation should be non-irritating, non-toxic, physically and chemically stable during storage and should have good skin feel [29, 30].

Skin Structure and Penetration Pathways

Anatomy of the Skin

The skin is a complex multi layered organ composed of three layers – epidermis, dermis and hypodermis or subcutaneous tissue. The most superficial layer, the epidermis, is made up of several layers: stratum corneum (SC), stratum lucidum (only in thick skin), stratum granulosum, stratum spinosum and stratum basale. The main barrier to drug permeation is the stratum corneum, which is composed of 15-20 layers of flattened, anucleate and terminally-differentiated keratinocytes (corneocytes) arranged in a lamellar lipid matrix. The lipid matrix is arranged in a 'bricks and mortar' structure, with corneocytes (bricks) surrounded by intercellular lipids (mortar), that are mainly ceramides, free fatty acids and cholesterol [31, 32]. Below the epidermis is the dermis, which has a rich vascular supply, lymphatics, nerve endings, hair follicles and sweat glands. Transdermal Drug Delivery relies on drugs that are successful in penetrating the epidermis and making their way into a dermal capillary and thus into systemic circulation. Hypodermis is composed mainly of adipose tissue, which soaks up lipophilic drugs, acts as a thermal buffer and provides mechanical protection [33, 34].

Routes of Drug Permeation

There are three possible routes through which drug molecules can penetrate the skin. The transcellular (intracellular) route is the pathway through which a drug moves directly across the corneocytes, and across the lipid matrix in an alternating aqueous-lipid environment, and is suitable for both lipophilic and hydrophilic drugs [35]. Yet, it is regarded as minor pathway because corneocytes are very resistant. The intercellular (paracellular) route is drug diffusion across the continuous intercellular spaces that are filled with lipid. This is the dominant route for most drugs, especially lipophilic drugs, and is the target of most permeation enhancement strategies. The transport of drugs via the appendageal route is through hair follicles, sweat glands and sebaceous glands, and they cover about 0.1% of the total skin surface. It is a small route, but especially significant for ions, macromolecules and nanoparticles which are not easily able to penetrate intact stratum corneum [36, 37].

Factors Affecting Skin Permeation

Many factors, both physiological and physical, control the rate and extent to which a drug penetrates the skin. The ideal candidates for topical delivery need to have the following drug physicochemical properties: a molecular weight of less than 500 Da, a log P (octanol-water partition coefficient) in the range 1-3, reasonable aqueous solubility to enable drug release and lipophilicity to facilitate partitioning into the stratum corneum. Thermodynamic activity of the drug in the vehicle, the nature and concentration of excipients, pH and penetration enhancers are formulation factors [38]. The permeation behavior is significantly affected by several biological factors including skin age, hydration status, temperature, application site, and possible presence of a skin disease (e.g. psoriasis, eczema) [39].

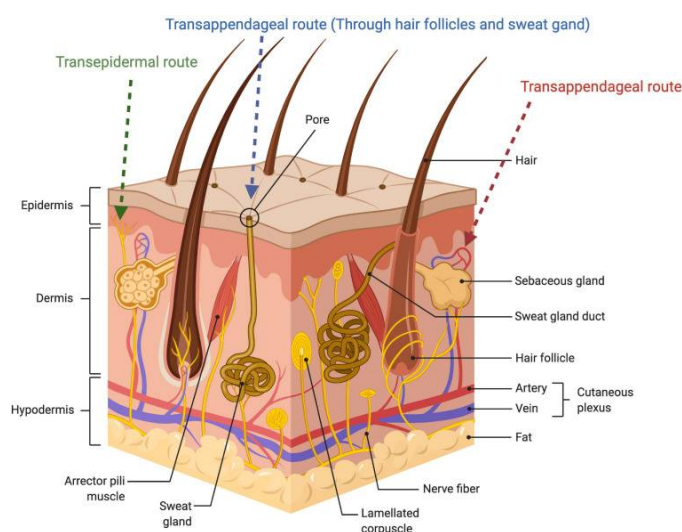


Figure 2: Structure of Human Skin and Major Drug Permeation Pathways

How Nanoemulgel gets past skin barriers

Nanoemulgel provides a number of synergistic mechanisms that overcome the drawbacks of the topical formulations. The smaller size of the dispersed droplets (20 to 200 nm) allows deeper penetration into skin appendages, such as hair follicles, that could be used to achieve depot effects for sustained drug release [40]. Nanodroplets have a large interfacial surface area which leads to a faster and more efficient drug partitioning in the skin lipids and thus increases the concentration gradient for drug permeation. The surfactants as ingredients in the nanoemulsion formulation can be regarded as chemical penetration enhancer because it can disrupt the organized lipid bilayer of the stratum corneum, which makes stratum corneum become more fluid and penetrable [41, 42]. The occlusive effect of the gel matrix decreases transepidermal water loss (TEWL), hydrates the stratum corneum and increases drug permeation even more. In addition, it raises the thermodynamic activity of the drug in the oil nanodroplets, thereby promoting the permeation of the drug through the skin.

FORMULATION OF NANOEMULGEL

Excipients and Preformulation Studies.

The preformulation studies are the foundation of rational development of a nanoemulgel. The initial phase of the process is a detailed examination of drug physicochemical properties, such as the ability to be soluble in different oils, surfactants and co-surfactants to determine the best components for the core of the nanoemulsion. Oils and the surfactant system are screened by performing an equilibrium solubility study with the saturation shake flask method. To ensure that potential incompatibilities are ruled out that could affect stability or efficacy the drugs and excipients are tested for compatibility using differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and X-ray diffraction (XRD). Typically, pseudo-ternary phase diagrams are drawn to determine the range of component ratios that give a nanoemulsion existence zone for a specific oil-surfactant-co-surfactant-water system [43].

Preparation of Nanoemulsion

High-Energy Methods

The high energy emulsification method is one such method that employs mechanical energy to break the dispersed phase into nanoscale droplets. One of the most popular methods is high pressure homogenization (HPH) in which the pre-emulsion is passed under high pressure (100-2000 bar) through a small gap, causing significant shear, cavitation and turbulence, and achieving droplet sizes in the nanometer range. Microfluidisation is a process which uses a microfluidizer to inject and collide two fluid jets at high velocity against one another or against a wall to obtain a very uniform nanoemulsion (PDI values < 0.2). With the power of high frequency ultrasonic wave (20-100 kHz), cavitation effect is generated, which breaks large droplets into nanodroplets⁴⁴. These approaches yield a great uniformity at the nanoscale with low droplet sizes, but need specialized equipment, create heat (which could jeopardize heat-sensitive drugs) and might be difficult to scale up into large scale production.

Low-Energy Methods

Low-energy emulsification methods make use of the natural physicochemical properties of the oil-surfactant-water system to spontaneously or by controlled transition to emulsification form a nanoemulsion without employing a high mechanical energy input. In spontaneous emulsification or solvent injection, the rapid injection of an oil phase containing solvent (organic phase) to the water phase leads to the formation of a spontaneous nanoemulsion, which is caused by the turbulence created at the interface by diffusion of the solvent [45]. The Phase Inversion Temperature (PIT) method is based on the temperature-dependence of hydrophilicity of non-ionic surfactant, which is zero at the PIT and fine O/W nanoemulsion is formed by a rapid cooling down below the PIT. The solvent diffusion method is an organic solvent, which is partially miscible with water, is quickly diffused into the aqueous phase, causing the formation of supersaturated conditions and spontaneous nucleation of nanodroplets. The low-energy methods are useful because they are easy to perform, have low energy input and can be scaled up, but are sensitive to temperature and composition variations, and component ratios must be optimized precisely [46].

Preparation of Gel Base

The gel base consists of the gelling agent that is dispersed in the water part of the formulation at the appropriate concentration. In gels made with Carbopol, the polymer is slowly dispersed in purified water, with moderate stirring to prevent forming lumps, and then is fully hydrated, neutralized with an appropriate alkali (usually triethanolamine or sodium hydroxide) to produce the desired pH (around 6-7) and allowed to gel by ionization of carboxylic acid groups and electrostatic repulsion between polymer chains. Usually, the cellulosic gelling agents like HPMC are hydrated in hot water, cooled to room

temperature and then the pH is adjusted to the desired level. Natural gums based gels are made by adding water slowly to gums, mixing and heating under defined conditions [47].

Incorporation of Nanoemulsion into Gel Base

It is now necessary to incorporate the prepared Nanoemulsion into the Gel Base. The homogeneous mixing of prepared Nanoemulsion in the gel matrix is called the incorporation step. This can be done by continuous slow stirring of the nanoemulsion dropwise at room temperature and ambient conditions into the pre-formed gel base to avoid droplet coalescence or phase separation. The stirring speed and time should also be controlled so that the mechanical stress does not destroy the nanodroplet structure. In some formulations, the gel components, (polymers, neutralizers) are added directly to the aqueous phase of the nanoemulsion during its preparation as opposed to preparing the gel separately [48]. The ratio of nanoemulsion to gel base is one of the most important optimization parameters that can affect various properties of the released drug such as release rate, viscosity and spreadability of the final formulation.

Optimization Techniques

Systematic optimization of nanoemulgel formulation is widely used with the help of statistical design of experiments (DoE) approaches. Box-Behnken Design (BBD) is a 2^3 fractional factorial response surface design that allows for the evaluation of the effects of three or more variables at three levels, with the minimum number of experiments and yet yields a quadratic response surface model. The CCD design has axial points added to an existing factorial design in order to estimate curvature and therefore obtain a better precision model. D-optimal designs are a set of computer designs which maximize the determinant of the information matrix; they are appropriate for irregular design spaces or design situations where there are restrictions on how factors may be combined [49]. ICH Q8 guidelines recommend a science-based and systematic framework for formulation development, known as the Quality by Design (QbD) framework. QbD includes determination of Critical Quality Attributes (CQAs) like droplet size, PDI, zeta potential, drug release and permeation flux; Critical Material Attributes (CMAs), for example, oil type, surfactant concentration; and Critical Process Parameters (CPPs), for example, homogenization pressure and speed. Identification and mitigation of risks are done through the use of risk assessment tools like Fishbone (Ishikawa) diagrams and Failure Mode and Effect Analysis (FMEA). Regulating flexibility is given by the definition of the Design Space that is the range of possible combinations of input parameters guaranteed to achieve product quality. When formulating a pedicure, consider the stability of the product [50]. There are a large number of physicochemical instability mechanisms that can be encountered in nanoemulgel systems. The process of Ostwald ripening is due to Laplace pressure differences between droplets of different sizes, and results in the continuous diffusion of molecules from smaller droplets in the continuous phase to larger droplets. This can be reduced by adding an 'Ostwald ripening inhibitor' which is a highly water insoluble oil (e.g. hexadecane) and/or by using an oil that has a low aqueous solubility. When droplets collide, coalescence occurs if droplet surfaces have high adhesion forces, which can be avoided by the use of effective surfactant stabilization and high zeta potential. Flocculation is the reversible tendency to aggregate, caused by attractive inter-droplet forces, that can be reduced by providing sufficient electrostatic / steric forces of repulsion. Gel matrix is high in viscosity, which prevents creaming or sedimentation caused by difference in density between dispersed and continuous phase. Recommendations for enhancing stability involve optimizing the amount of surfactant, the use of multiple primary and secondary emulsifiers, and the use of proper gelling agents which can maintain stability during storage [51].

Characterization of Nanoemulgel

Physicochemical Characterization

Comprehensive physicochemical characterization is essential to confirm the quality and performance of nanoemulgel formulations and to establish correlations between formulation parameters and therapeutic outcomes.

Table 1: Physicochemical characterization parameters for nanoemulgel formulations.

Parameter	Method/Instrument	Acceptable Range
Droplet Size	Dynamic Light Scattering (DLS)	20–200 nm
Polydispersity Index (PDI)	Dynamic Light Scattering (DLS)	< 0.3
Zeta Potential	Laser Doppler Electrophoresis	$\geq \pm 30$ mV
pH	Calibrated digital pH meter	5.0–7.0
Viscosity	Brookfield Viscometer	1000–50,000 mPa·s
Refractive Index	Abbe Refractometer	~1.33–1.45
Electrical Conductivity	Conductivity meter	Varies by system
Drug Content	HPLC / UV Spectrophotometry	95–105% of label claim
Entrapment Efficiency	Ultracentrifugation + HPLC	> 80%

Morphological Characterization

By using morphological examination, the nanoemulgel has been visually confirmed with the morphology of the nanodroplets to confirm their size, shape, and internal structure. Transmission Electron Microscopy (TEM) involves directing a beam of electrons through a very thin sample to see it at the nanoscale with a resolution of the images produced. It was used in this research to showcase the spherical shape and size distribution of nanodroplets. The chemical composition of the sample does not need to be considered for the Scanning Electron Microscopy (SEM) technique, which scans the sample surface with a focused electron beam generating topographic images; It is not ideal for a liquid dispersion but is useful for the freeze-dried nanoemulgel or dried nanoparticles loaded with drugs. Additionally, the 3-dimensional topographical images of the surface obtained by Atomic Force Microscopy (AFM) by deriving forces between the sharp probe tip and the surface of the sample, complimentary information on surface roughness and droplet morphology was obtained [52]. Cryogenic TEM (cryo-TEM) is now generally employed to obtain images of nanodroplets in "native" hydrated conditions, without any fixation artifacts and without any staining artifacts that would normally affect TEM imaging. Cryo-TEM provides the best representation of the nanoemulsion droplet morphology.

Drug Content and Entrapment Efficiency

dose in a suitable drug solvent system followed by the estimation by HPLC/UV-Vis spectrophotometry. HPLC offers higher specificity, sensitivity and accuracy, especially useful in complex formulations, which can contain several excipients that may co-absorb at UV, will be better responded by HPLC. The entrapment efficiency (EE%) is ratio of the amount of the drug entrapped in the nanodroplet to the total amount of drug in the formulation. The free (unentrapped) drug in the aqueous phase is separated from nanodroplet encapsulated drug by ultracentrifugation (usually between 15,000-20,000 rpm for 30-60 mins), after which the drugs are quantitatively determined in the separated nanodroplet and aqueous fraction. The quality attribute of high entrapment efficiency (>80%) is crucial because it indicates the formulations ability to keep the drug in the nanodroplets throughout storage and application [53].

Spreadability and Extrudability

Spreadability is a clinically significant property defining how easily a topical formulation can be evenly applied on the skin surface. It is evaluated through the parallel plate method which involves a known amount of the formulation being placed between two glass plates, a standard weight is placed on top of the formulation and the spreading distance or area is measured after a certain time. The higher the value of spreadability the easier the application. Extrudability is determined by the length of gel that can be extruded from a tube under a specified weight during a set amount of time and is a measure of ease in which the formulation can be extruded. The formulation properties must be balanced with viscosity so that it can be applied uniformly without it being too fluid or stiff [53].

In Vitro Drug Release Studies

The in vitro drug release studies give important information on the rate of drug release from the nanoemulgel as well as its prediction in vivo performance. The most widely used method is the Franz diffusion cell apparatus which consists of the donor compartment filled with the nanoemulgel formulation and the receptor compartment filled with the release medium (either phosphate buffer, pH 7.4 or 6.8) or a biological membrane (synthetic membrane such as cellulose acetate or polysulfone). Aliquots are taken from the receptor compartment at regular time intervals and subsequently analyzed by HPLC or UV spectrophotometry. Dialysis bag method is a simpler method for preliminary screening by enclosing the formulation in dialysis bag and submerging it in the release medium. The mechanism of the drug release is explained through mathematical kinetic models that are fitted to the drug release data. The zero-order kinetic is that in which the drug is released in a steady rate - it does not depend upon the drug concentration - which is suitable for sustained releases. First-order kinetics is a drug release which is directly proportional to the concentration of the remaining drug. For matrix systems drug release can be described by the Higuchi model, which is based on Fick's law of diffusion. The Korsmeyer-Peppas power law model was used to correlate the release of the drug with the time, and release exponent (n) values were less than 0.5, between 0.5 and 1.0, or greater than 1.0, suggesting Fickian diffusion, anomalous (non-Fickian) transport, and Case II (swelling controlled) transport, respectively [53, 54].

Ex Vivo Skin Permeation Studies

If excised human cadaver skin or animal skin (rat, pig, rabbit) is used in Franz diffusion cells, permeation data obtained are more physiologically relevant than the data obtained from synthetic membranes. Prior to formulation application to the surface of the stratum corneum, full thickness or dermatomed (300–400 μm) skin is equilibrated in the receptor medium. The permeation parameters calculated: the steady-state permeation flux (J_{ss} , $\mu\text{g}/\text{cm}^2/\text{h}$), the lag time (T_{lag} , h), the permeation coefficient (K_p , cm/h) and the enhancement ratio (ER), defined as the ratio between the permeation flux

of the nanoemulgel and a reference formulation [55]. Local abattoir pig ear skin is most commonly used as a human skin surrogate as it is anatomically and histologically similar to human skin.

In Vitro Skin Retention Studies

Skin retention studies measure the extent of drug remaining in each layer of the skin following application, and are useful in determining the local dermatropic effects. Tape stripping is a method based on the sequential removal of layers of SC with adhesive tape after a specific application time that allows to extract and quantify the amount of drug contained in each strip, thereby providing also a drug distribution profile as a function of the depth. Confocal Laser Scanning Microscopy (CLSM) allows the visualization of the penetration of a drug into the layers of the skin (three-dimensional), without damage to the skin, using fluorescent labelled drugs or markers by scanning the tissue with a laser beam [56].

Rheological Studies

Rheological characterization provides basic information regarding the mechanical properties and flow behavior of Nanoemulgel, which directly relates to its application performance and stability, as well as its drug release behavior. Steady-state flow measurements relate shear stress to shear rate (flow curves), and most nanoemulgel formulations showed the pseudoplastic (shear thinning) flow characteristics, in which the viscosity of the product decreases as shear rate increases (which is helpful to apply) but does not decrease too much (evaluating viscosity at rest). Another important property is the phenomenon of thixotropy, namely the viscosity regaining the value it had prior to introducing shearing, when it is stopped. Dynamic oscillatory measurements (frequency sweeps, amplitude sweeps) measure the viscoelastic properties of the gel matrix, the storage modulus (G' , elastic) and the loss modulus (G'' , viscous). Elastic behaviour ($G' > G''$) is desirable for maintaining the structural integrity under storage conditions, which is called dominant elastic behaviour [10].

Stability Studies

The physical, chemical and stability of nanoemulgel formulation under the given storage conditions is tested via long-term and accelerated stability studies as per ICH Q1A(R2). Usually accelerated stability tests are carried out for 6 months at $75\% \pm 5\%RH$ and $40^\circ C \pm 2^\circ C$ and intermediate stability tests are made at $30^\circ C \pm 2^\circ C$ and $65\% \pm 5\%RH$ for 6 months. Droplet size, PDI, zeta potential, pH, viscosity, drug content, organoleptic properties (color, odor) and EE are key stability parameters monitored. Freeze-thaw cycling (three to six cycles between $-20^\circ C$ and $+25^\circ C$) is done to stress the formulation at temperatures extremes, and can expose the formulation to phase separation, Ostwald ripening, crystallisation. Photostability studies are conducted for drugs that are sensitive to light [28].

Safety and Irritation Testing

The topical formulations containing the nanoemulsions should be tested for safety using suitable in vitro/in vivo tests. The Hen's Egg Chorioallantoic Membrane (HET-CAM) assay is an in vitro test of ocular and skin potential for irritation that uses the Hen's Egg chorioallantoic membrane (CAM) to evaluate vascular responses (lysis, hemorrhage, coagulation) [55]. *In vivo* Draize rabbit or guinea pig skin irritation testing is a regulatory standard for assessing dermal irritation; however, this is being superseded by in vitro testing models like EpiDerm™ reconstructed human epidermis. Cytotoxicity assays (e.g. MTT assay, a metabolic activity assay) with the HaCaT keratinocytes cells, HEK293 cells as representative cell lines, provide cell level safety data in the presence of the formulation. Formulation is considered non-irritating when primary irritation index (PII) obtained from Draize test score is less than 0.5 [56].

MECHANISM OF DRUG RELEASE AND PERMEATION ENHANCEMENT

Mechanisms of Drug Release from Nanoemulgel

The release of these drugs from the nanoemulgel depends on the interactions between the nanoemulsion core and the gel swelling matrix, and the drugs release can be controlled by the diffusion, partitioning, and matrix erosion/swelling mechanisms. In diffusion-controlled release, the drug diffuses from the oil nanodroplets across the oil-water interface into the aqueous gel phase followed by diffusion from the gel phase to the skin surface, by diffusiphobic gradient. The rate the drug will be released from the formulation is critical and will depend on the partition coefficient between the oil droplets and the aqueous phase (K_o/w), which is a number that indicates how much the drug will stay in the oil phase or move to the aqueous phase. In gel matrices, the erosion/swelling effect is dominant in which drug molecules are released due to the swelling of the polymer chains during hydration and/or the creation of non-contractive drug pores as a result of swelling [57].

Permeation Enhancement Mechanisms

Nanoemulgel has several complementary mechanisms that increase the permeation of drugs across the skin. Surfactants and cosurfactants in the nanoemulsion fluidize the intercellular lipid bilayers of the stratum corneum, and cause the disordering of the ordered lipid structure and the formation of transient

channels which allow drugs to be transported through the skin. The thermodynamic activity enhancement mechanism describes the enhancement of drug solubility in the oil nanodroplets, which leads to an increase in the driving force for partitioning into the skin due to an increase in the chemical potential (thermodynamic activity) of the drug in the vehicle. The nano-droplet fusion mechanism states that nanodroplets are directly deposited onto the surface of the skin, and are then able to fuse with the lipid bilayers of stratum corneum, allowing for the delivery of drug molecules and lipid penetration enhancers directly into the intercellular lipid domain [58]. Also, the hydration of stratum corneum due to the presence of the aqueous gel matrix causes expansion of the aqueous channels in the corneocyte protein matrix, thus enhancing the permeability of the stratum corneum.

Mathematical Models for Release Kinetics

The Korsmeyer-Peppas model ($M_t/M_\infty = Kt^n$) is most commonly used for the release data of nanoemulgels and gives mechanistic insights into the release by means of the diffusion exponent n . The values of the parameter n are equal to 0.43 (Fickian diffusion), between 0.43 and 0.85 (anomalous transport), and $n = 0.85$ (Case II transport) for spherical geometries [55]. A model called Peppas-Sahlin is used to decompose the effect of Fickian diffusion from that of Case II relaxation. Weibull model is an empirical fit to cumulative release data. In practice, the model with the highest value of the correlation coefficient (R^2) and the lowest sum of squares is used and the mechanistic model will give more understanding than a purely empirical description of the model. AI/ML methods are now being investigated to model drug release from complex nanosystems predictively [53].

APPLICATIONS OF NANOEMULGEL

Anti-inflammatory and Analgesic Applications

Treatment of inflammatory diseases like rheumatoid arthritis, osteoarthritis and musculoskeletal pain is one of the most researched modes of action of Nanoemulgel. Non-steroidal anti-inflammatory drugs (NSAIDs) are good candidates for topical nanoemulgel delivery because they have been reported to have many gastrointestinal side effects on oral administration. Diclofenac sodium nanoemulgel has been extensively tested and proven to possess a much stronger anti-inflammatory activity, have a more rapid onset of action and longer duration of action than conventional diclofenac gels and the marketed product Voltaren Emulgel®. Ketoprofen nanoemulgel has been shown to exhibit greater permeation flux (3-5 fold higher than control gel) and greater efficacy in pain reduction models of carrageenan-induced paw edema. The Ibuprofen nanoemulgel formulations prepared with oleic acid as oil-phase and with Tween 80 as surfactant have demonstrated high entrapment efficiencies (> 90%) and prolonged release characteristics of up to 12 hours [59]. These formulations collectively indicate the potential of this Nanoemulgel formulation for therapeutic drug concentrations in articular and periarticular areas, while minimizing systemic exposure.

Antifungal Applications

Poor penetration of antifungal agents through the skin and the need for long-term treatment periods limit the use of topical antifungal drugs in the treatment of dermatomycoses (tinea pedis, tinea corporis, candidiasis, onychomycosis). Nanoemulgel has been found to be very promising in the area of topical delivery of the azole anti-fungals. The advantage of fluconazole nanoemulgel formulations is that they show significantly larger inhibition zone against *Candida albicans* in antifungal efficacy testing, excellent skin permeation performance compared to fluconazole gel and better retaining capabilities in the stratum corneum. The nanoemulgel formulation (Clotrimazole Labrafil M 1944 CS, surfactant Cremophor EL) showed potent antifungal activity with 4-fold more permeation of the drug than that of marketed drug. In experimental animal models of cutaneous candidiasis, ketoconazole nanoemulgel has shown greater efficacy than conventional ketoconazole cream and led to a marked decrease in fungal burden. The nanodroplets can penetrate the hair follicles and nail structure in particular is of great benefit to fungal infections of the hair and nails (onychomycosis) [60].

Antibacterial Applications

Nanoemulgel has been investigated for an innovative topical, antibacterial wound and skin surface colonization treatment. The greater activity for MRSA reported with muiprocin nanoemulgel formulations than with the marketed Bactroban® ointment appears to be due to an increase in bioavailability of the drug at the point of infection. The nanoemulgel formulation of fusidic acid has demonstrated higher antibacterial activity and skin permeation as compared to the conventional formulation of the cream in the treatment of impetigo and secondarily infected eczema. Formulations of natural antimicrobial ingredients like thymol, carvacrol and eugenol, known as nanoemulgel have emerged as an alternative to synthetic antibiotics with their wide-spectrum antimicrobial activity and lower tendency to induce drug resistance. Nanoemulgels with growth promoting phytoconstituents and antibacterial agents are able to

give dual action therapy for wound healing applications because of their antibacterial activity and growth promoting constituents [60].

Anticancer and Skin Cancer Applications

Case: use of topical chemotherapy in non-melanoma skin cancers, pre-cancer and superficial malignancies is a clinically relevant application of nanoemulgel technology. It has been found that 5-Fluorouracil (5-FU) is a more effective topical treatment for actinic keratoses and superficial basal cell carcinoma, when formulated as a nanoemulgel compared to the usual formulation which is a solution. 5-Fluorouracil (5-FU) has been found to be a more effective topical treatment for actinic keratoses and superficial basal cell carcinoma, when formulated as a nanoemulgel rather than a solution, due to improved skin penetration and reduced systemic toxicity. Nanoemulgel formulations of 5-FU have been found to offer skin permeation 3–5 fold higher than conventional 5-FU cream, and were shown to achieve higher 5-FU concentrations in the epidermis. Curcumin, a natural polyphenol that has already been documented as anticancer, anti-inflammatory and antioxidant compound, is extensively formulated as nanoemulgel as a result of its low aqueous solubility and the low degree of photostability. Nanoemulgel of paclitaxel has been evaluated in the treatment of Kaposi's Sarcoma and other skin cancers [61]. The formulations show improved in vitro efficacy against tumor cells and better in vivo efficacy against tumors in animals with human tumor xenografts, and very low systemic exposure to the drugs.

Antiacne Applications

One of the most common dermatological diseases worldwide, acne vulgaris has a complex pathogenesis in which follicular hyperkeratinization, hypersecretion of sebum (lipids), colonization of the follicles with *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*) and inflammatory response play a role in approximately 85% of people aged 12–25 years. Nanoemulgel is a novel topical vehicle for antiacne products. Tretinoin (all-trans retinoic acid) nanoemulgel has been proven to provide a higher follicular penetration, less skin irritation than the normal tretinoin gel and the most effective comedolytic and anti-inflammatory effect. The purpose of this product is to provide an antimicrobial effect with reduced bleaching effect of benzoyl peroxide (BPO) nanoemulgel against *C. acnes*. Nanoemulgels may also contain essential oils, such as tea tree oil (*Melaleuca alternifolia*), which have become interesting with regard to their natural antiacne activity, being both antibacterial and anti-inflammatory and with greater penetration of the skin via the follicular pathway [62].

Anti-psoriatic Applications

Psoriasis is a chronic autoimmune inflammatory skin condition that is associated with hyperproliferation of the epidermis and altered keratinocyte differentiation, in addition to dermal inflammation, and affects ~2–3% of the world's population. For mild to moderate psoriasis the initial therapeutic approach is topical therapy, although the hyperkeratotic plaques are very resistant to drug penetration. Methotrexate nanoemulgel has been found to be highly effective at overcoming this increased barrier, showing 3–8 fold enhanced permeation of methotrexate through psoriatic skin in comparison to formulation in gel, and better clinical outcomes with lower systemic toxicity in imiquimod-induced psoriatic mouse models. A higher potency corticosteroid formulation, clobetasol propionate nanoemulgel has been shown to have similar efficacy in the treatment of psoriasis while inducing significantly less skin atrophy than marketed clobetasol cream due to a controlled release profile that allows for therapeutic levels of drug to be maintained without this increasing skin atrophy [37].

Herbal and Phytoconstituent-Based Nanoemulgels

Recently, nanoemulgel technologies have been gaining popularity due to the growing trend toward natural-based therapies by consumers and the lack of bioavailability of many phytochemicals. Curcumin nanoemulgel is perhaps the most widely studied herbal nanoemulgel material, which has been found to have significant greater skin permeation, anti-inflammatory, wound healing and anticancer activities than regular curcumin formulation. Quercetin nanoemulgel is known as a “nano” formulation that possesses greater antioxidant and anti-inflammatory activity as well as greater deposition in the skin. CBD nanoemulgel has been receiving a substantial amount of commercial and scientific attention to treat inflammatory skin diseases, neuropathic pain, and anxiety due to their increased permeation and long-lasting effect³⁸. Resveratrol nanoemulgel has been formulated for its high antioxidant, photoprotective and anti-aging mechanisms. Green nanoemulgels using plant based surfactant (such as saponin, lecithin) and biodegradable oils is an environmentally friendly method of topical drug delivery [39, 61].

Cosmetic and Dermatological Applications

The cosmeceutical industry has warmly welcomed nanoemulgel technology in order to create innovative, skincare products that fall somewhere between cosmetic and pharmaceutical. Nanoemulgels of these active ingredients – kojic acid, arbutin, niacinamide and tranexamic acid – have shown to be more effective in inhibiting melanogenesis and promote more uniform skin tone than standard topicals. Anti-

aging nanoemulgels containing retinol, peptides, hyaluronic acid and vitamins C and E allow the delivery of anti-wrinkle and pro-collagen synthesis agents to deeper dermis layers where the production of collagen takes place through fibroblast activity. Nanoemulgels containing UV filters can provide photoprotection to the skin via UVA/UVB filters in the form of zinc oxide, titanium dioxide and organic UV absorbers, with the advantage of having a positive effect on the sense of feel, transparency and reduced photodegradation of the UV filters within the formulation. A compromised skin barrier function is seen in situations like atopic dermatitis and dry skin, and moisturizing nanoemulgels containing ceramides, fatty acids and cholesterol restore that compromised barrier function [61, 62].

Transdermal Applications

In addition to its topical local effect, nanoemulgel has been shown to be of great potential to deliver therapeutic systemic concentration using the skin as a non-invasive pathway to reach the systemic circulation, particularly for drugs which require a long-lasting systemic effect. One application where hormone replacement therapy is particularly appropriate is for the transdermal delivery of therapeutically effective plasma concentrations, as evidenced by the case of estradiol nanoemulgel, which has shown effective and sustained transdermal delivery that mimics the plasma concentration achieved with oral hormone replacement therapy (HRT) but with a significantly lower first-pass effect and thus less associated cardiovascular and hepatological risk⁶³. Testosterone nanoemulgel is a patient friendly alternative for managing hypogonadism that is associated with higher concentration of plasma testosterone with lower half-life compared to testosterone injections. Some antihypertensive drugs, like amlodipine and nifedipine, have been prepared into nanoemulgels, which have shown some controlled permeation of drug and prolonged antihypertensive activity in animal models and hence can be used in the management of chronic hypertension [61, 62].

Recent Advances and Novel Approaches

In recent decade, the research area of "nanoemulgel" has seen incredible technology advances due to the interaction between nanotechnology, material science, and pharmaceutical engineering. One of the most promising advancements in the field is the stimuli responsive nanoemulgels, which can release a drug on demand and/or on site through physiological/stimuli-induced mechanism. By using pH-sensitive polymers like Eudragit S100 or Carbopol, pH-responsive nanoemulgels selectively release drugs in response to the acidic pH environment of inflamed or infected skin. Thermoresponsive polymers, such as Pluronic F127 or poly(N-isopropylacrylamide) (PNIPAM), are used to create a nanoemulgel that changes properties, from gel to sol, at the lower critical solution temperature (LCST), and which releases a drug on local temperature increase. Solid nano emulgels, known as nanostructured lipid carrier (NLC)-based nanoemulgels, are made with solid lipids along with liquid oils, resulting in semi-solid nanoparticles that can offer better protection for the drug against chemical degradation and improved stability during storage than conventional nanoemulgels can. Self-nanoemulsifying drug delivery systems (SNEDDS) in gel matrices (SNEDDS-gels or self-nanoemulsifying gels) provide thermodynamically stable self-emulsifying systems that provide in situ formation of nanoemulsions on application or dilution in the aqueous secretion of the skin. The combination of microneedle technology with the use of nanoemulgel is a "frontier" technique, wherein the physical permeation enhancement of the microneedle technology allows the penetration of high molecular weight drugs, biologics and nanoparticles which would be otherwise impermeable to the intact skin. To realize personalized nanoemulgel patches with precisely controlled drug loading, geometry and release kinetics that fit the needs of individual patients, 3D printing technology has been used. In recent years, with increasing environmental and regulatory concerns on the toxicity of the synthetic excipients, the green synthesis methods with plant-derived surfactants, gelling agents based on biopolymers and biodegradable oils are at the forefront of the development of nanoemulgels for sustainable production [8, 63].

CHALLENGES AND LIMITATIONS

Although great strides have been made in the field of nanoemulgel, there are still an array of challenges to be overcome in order for this technology to be adopted widely in the clinic and ultimately make it to market. Scales-up from laboratory conditions to the industrial scale will involve significant engineering challenges, especially when dealing with high-energy emulsions which require specialized equipment to be able to produce the same nanodroplet size and distribution in large-scale quantities. The energy input, process conditions and processing times have to be carefully controlled to assure the reproducibility from batch to batch. One issue that continually exists is the lack of stability during scale-up, storage and distribution as nanoemulsions are thermodynamically metastable and prone to Ostwald ripening, coalescence and phase separation, particularly in warm and humid environments as encountered in transporting and storing in tropical and subtropical regions. Uncertainties in regulatory issues are

important for the commercialization of nanotechnology-based drug delivery systems. There is uncertainty and higher cost & time involved in regulatory submissions as there are no specific harmonized regulatory guidelines from the major regulatory bodies FDA, EMA & CDSCO for characterization, safety assessment & approval of nanomedicine. High levels of necessary surfactant and cosurfactant are required for nanoemulgel formulation that carries with it toxicity concerns, which must be fully evaluated by exhaustive preclinical and clinical safety studies to assess skin sensitization, irritation and systemic toxicity potential⁴. The classic in vitro-ex vivo permeation/ex vivo release studies performed on excised human skin often are not able to reflect the complexity of in vivo PK of topical formulations, and the in vitro-in vivo correlation (IVIVC) is therefore limited. Costs of the specialized equipment, high quality-grade emulsification components and extensive characterization requirements can make nanoemulgel products inaccessible and/or unaffordable in LMICs. Careful formulation optimization is required to take into account patient acceptability factors like residual greasiness of oil phase, potential stinging effect due to high surfactant concentration and cosmetics elegance considerations [13].

REGULATORY CONSIDERATIONS

Nanoemulgel products are being regulated by a changing framework as the regulatory landscape evolves with the rise in nanomedicine and engagement of regulatory agencies with issues relating to nanotechnology. Stability studies are required to meet the requirements of ICH Q1A(R2) that outline stability conditions, time points and parameters for use in stability protocols for product registration. ICH Q1B contains guidance on the testing of photostability of light-sensitive formulations. ICH Q8(R2) guidelines for pharmaceutical development are the scientific and regulatory guidance for the development of nanoemulgel using Quality by Design (QbD) approach. The US Food and Drug Administration (FDA) has issued a number of guidance documents relevant to nanotechnology-based products, including 'Guidance for Industry: Drug Products, including Biological Products, that Contain Nanomaterials' (2022), which provides guidance on the characterization, manufacturing controls, and safety assessment of products containing nanomaterials. The FDA calls for comprehensive physicochemical characterization of nanomaterials, evaluation of biological interactions, and evaluation of potential immune responses. Guidelines for the development of nanomedicines have been provided by the European Medicines Agency (EMA), one of which is the 'Guideline on the Characterisation of Nanomaterials as Applied to Medical Products' (ENTR/F/2/SF/dn D(2011) 35810), which outlines the characterisation requirements for nanomedicines that have been submitted for marketing authorization [38]. World Health Organization (WHO) has been actively involved in the field of regulatory harmonization of nanomedicines, as the need for internationally consistent regulatory frameworks for safe innovation and global access is paramount. The Central Drugs Standard Control Organization (CDSCO) has published a Draft Guidelines for Evaluation of Nanomedicine Drug Products, which provides regulatory pathway and data requirement for approval of topical nanomedicine drug products in India. The general safety data requirements involve in vitro cytotoxicity, skin irritation and skin sensitization tests, genotoxicity studies, repeated dose dermal toxicity studies, and for systemic delivery applications, extensive toxicokinetic and toxicokinetic studies [64].

FUTURE PERSPECTIVES

Collisions between personalized medicine, advanced manufacturing, biotechnology and sustainability trends put a bright future in nanotechnology ahead us and this type of technology – nanoemulgel is a perfect example. Personalized nanoemulgel therapy through the use of the novel concepts of pharmacogenomics, biomarker identification, and personal skin barrier characterization holds promise for personalized and tailored formulations to address individual genetic make-up, disease severity, and skin barrier type. New formulation optimization initiatives have been increasingly achieved using a combination of artificial intelligence (AI) and machine learning (ML) algorithms, which allow for the speedy screening of excipients combinations, prediction of the droplet size and stability based on the properties of the excipients and the identification of the optimal formulation process parameters from a large set of experiments — significantly shortening the formulation development timeline. The future of development of most of the topopreparations, from the point of their environment friendly formulation, will be associated with the use of relatively new nanoemulgels based on renewable, biodegradable and biocompatible gelling agents such as chitosan, HA, cellulose derivatives, plant gums, as well as natural emulsifiers. Theranostic nanoemulgels, where therapeutic drugs can be delivered and integrated diagnostics (such as imaging contrast agents or biosensors into the nanodroplet core) provide real-time monitoring of the efficiency of the drug delivery and response to the disease at the skin level, are an

innovative platform. Since the skin is well endowed with antigen presenting Langerhans cells and dendritic cells, the potential for delivering vaccine antigens to skin via nanoemulgel as an adjuvant and delivery system is a particularly interesting area of future research. Nanoemulgel's needle-free, painless and patient-friendly approach to vaccination could provide an alternative to traditional needle shot immunization. Development of widely accepted and internationally adopted characterization protocols and regulatory frameworks specifically developed for nanoemulgel and topical nanomedicine will be crucial for the rapid translation of the groundbreaking laboratory results to approved clinical products that can be used by patients across the globe [65].

CONCLUSION

Nanoemulgel is a technologically innovative and clinically successful formulation to overcome the major drawbacks of traditional topical formulations. Nanoemulgel combines the advantages of both nanoemulsion and gel-based system, such as drug solubilization, permeation enhancement, and long contact time with the skin, with a better patient acceptability and acceptance, to obtain a best therapeutic activity for a wide range of dermatology and transdermal applications. All the literature analyzed in this article showed that the ability of the nanoemulgel to load the drug, permeate the skin, release the drug from the formulation, maintain physical stability with time and produce therapeutic effects in relevant experimental models in either in vitro or ex vivo systems are constantly superior to traditional topical formulations. It has been demonstrated in applications that cover a wide range of physicochemical properties, from lipophilic NSAIDs, antifungals, water-soluble chemotherapeutics, to natural polyphenols, and has been shown to be flexible with the incorporation of the entire range of modern pharmaceutical excipients. Although the issues of size, long-term use, regulatory clearance and full clinical validation are formidable hurdles to overcome systemically, there is widespread and strong research interest in this product, which appears to be becoming a mainstream platform for topical drug delivery. Thus, the technological bridge that connects innovation that takes place on the bench to bedside application is now positioned to correspond with the coming-of-age of nanoemulgels: combined with the four examples of formulation development and advanced characterization, stimuli responsive formulation and AI assisted formulation optimization, the next generation of nanoemulgels is set to be available in the near future, supported by sustainable manufacturing approaches. In the future, drug delivery via nanoemulgel technology will revolutionize the therapeutic approach to topical and transdermal drug delivery systems if pharmaceutical scientists, physicians, regulatory agencies and industry continue to work together in an interdisciplinary manner, in this decade.

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