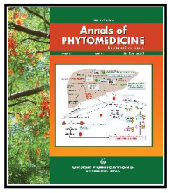
Annals of Phytomedicine 12(2): 239-245, 2023

DOI: http://dx.doi.org/10.54085/ap.2023.12.2.28

Annals of Phytomedicine: An International Journal
http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Review Article : Open Access

Nanoemulgel as an innovative platform for phytomolecules

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Article Info

Article history
Received 12 June 2023
Revised 30 July 2023
Accepted 31 July 2023
Published Online 30 December 2023

Keywords
Phytoconstituents
Bioavailability
Lipophilic drug
Nanoemulgel
Permeation enhancement

Abstract

The development of herbal remedies in the form of phytoconstituents, bioactive compounds, and extracts for healthcare has piqued the interest of both researchers and medical professionals. Around 80% of the world's population has profited from phytomolecules that consist of numerous attributes, including their nutritious composition and antioxidant, anti-inflammatory, and other therapeutic characteristics. However, lipophilic phytomolecules have various drawbacks, such as poor water solubility, permeability, stability at physiological pH, and poor absorption in GIT, limiting their bioavailability. Nanoemulgel as a good vehicle can overcome the above problems and have better patient compliance due to its noninvasive delivery, high penetration ratio, avoidance of gastrointestinal side effects, easy application, convenient spreadability, and stronger therapeutic and safety features than other topicals. Nanoemulgel is one of the novel topical delivery systems because it has two different release control systems, *i.e*., hydrogel and nanoemulsion. Due to the finely dispersed oil droplets in the gel phase, lipophilic drugs can be easily incorporated, thus enhancing permeability in several folds that improve the therapeutic efficacy of acne, psoriasis, fungal infection, inflammation, and rheumatoid arthritis. The formulation can also be delivered *via* ocular, vaginal, dental, and nose-to-brain routes for the treatment of local and systemic ailments such as alopecia, periodontitis, and Parkinson's disease. In the future, nanoemulgel could be recognised as a key and effective formulation for lipophilic drugs. This review highlights the properties, preparation methods, benefits, and characterization of nanoemulgel as a nanocarrier for drug delivery.

1. Introduction

The great advancement in the development of the poorly water-soluble drug emerged through extensive research in chemical synthetic methods. According to statistical sources, the percentage of poorly water-soluble new chemical entities is approximately 70%; they thus have lipophilic characteristics, poor oral bioavailability, variable intra- and inter-subject pharmacokinetics, and irregular absorption. It can be improved by the development of different delivery systems and chemical and/or physical changes to the drug moiety. Despite the fact that there are numerous drug delivery system strategies, lipophilic drug delivery systems such as liposomes, niosomes, solid-lipid nanoparticles, self-emulsifying formulations, and macro- and nanoemulsions have drawn a lot of attention (Amsa *et al*., 2022). Natural substances have become more important for therapeutic treatment in recent years due to their low toxicity. To achieve greater efficacy, the delivery of these phytoconstituents must be improved.

The oral route has a number of drawbacks, including gastrointestinal discomfort, poor bioavailability, inevitable side effects, systemic toxicity, and hepatic first-pass metabolism. The effectiveness of herbs in the human body can be increased through the use of novel strategies. Hence, a non-injurious, non-painful, and non-invasive topical drug delivery method can be a good solution to avoid all these problems and has benefits like enhanced bioavailability at the site, targeted site-specific drug delivery, decreased drug degradation, and better patient compliance. Traditional topical formulations like creams, lotions, and ointments have various drawbacks, such as stability, low spreadability, sticky texture, less permeability, and patient compliance. Nanoemulgels increase formulation efficacy, diffusion, safety, and stability (Sultana *et al*., 2022), reducing drug metabolism, as well as maintaining controlled steady-state distribution (Gannu *et al*., 2010).

2. Plant based phytoconstituents for topical therapies

In ancient China and Egypt, plant extracts made from seeds, flowers, leaves, roots, and fruits were widely used as medicinal compounds. Topical skincare treatments that contain plant-based bioactive components are thought to be much more effective, safe, and economical than synthetic ones. The secondary metabolites found in plants, such as phenolic acids, flavonoids, polyphenols, terpenoids, and amino acids, are abundant and beneficial (Lalitha *et al*., 2022; Sri Bhuvaneswari *et al*., 2022). Numerous studies have been conducted recently to understand the medicinal effects of certain herbs or to determine their isolated constituents for application in the pharmaceutical industry and clinical practise (Romes *et al*., 2021). Flavonoids, phenolic acids, and high-molecular-weight polyphenols are significant categories of beneficial

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phytoconstituents. Hydroxycinnamic acid and hydroxybenzoic acid are two examples of naturally occurring phenolic acids. Condensed polymers of catechins or epicatechins and hydrolyzable polymers of gallic or ellagic acids are examples of high-molecular-weight polyphenols, commonly referred to as tannins. Luteolin, quercetin, and catechins are only a few flavonoids that have been discovered to be more effective antioxidants than alpha-tocopherol, ascorbic acid, and beta-carotene (Malik *et al*., 2020). Curcumin, apigenin, silymarin, caffeic and ferulic acids, resveratrol, carnosic acid, and genistein are other plant-based phytoconstituents (Saraf and Kaur, 2010).

3. Factors influencing topical absorption of drug

3.1 Physiological factors

- Skin's lipid content
- Thickness of different layers of skin
- Density of hair follicles
- Skin pH
- Hydration of the skin
- Sweat gland density
- Blood flow
- Skin temperature (Ayub *et al*., 2007)

3.2 Physicochemical factors

- Partition coefficient
- Effect of vehicles
- Degree of ionisation
- Molecular Weight (<400 Dalton) (Ajazuddin *et al*., 2013)

4. Nanoemulsion

The nanoemulsion method is the most efficient drug delivery approach for the majority of medicines since it maximises effectiveness while minimising toxicity. A nanoemulsion system combines nanoranges of two immiscible liquids (water and oil) to form a homogenous solution by adding therapeutic drugs, surfactants, and/or co-surfactants. This thermodynamically stable system has a size range of 10-100 nm. Nanoemulsions improve oral absorption; they help in targeting poorly soluble drugs and also enhance the penetration of drugs through the skin, leading to faster drug processing at the site of action and fewer side effects (Shaji *et al*., 2012). Additionally, the smaller the particle size, the more medication is added to the mixture, which improves the thermodynamics towards the skin. Thus, the nanoemulsion is formulated as a spontaneous emulsifying method, which provides several advantages over other carriers like polymeric nanoparticles and liposomes, including low cost for formulation, a high hydrophilic and lipophilic drug loading system, a longer shelf-life, and an enhanced therapeutic effect (Bhaskar *et al*., 2009).

4.1 Advantages of nanoemulsion

- Nanoemulsions do not have emulsion defects like flocculation, coalescence, creaming, or phase separation.
- Nanoemulsion is an effective delivery device owing to its enormous surface area and free energy.
- Nanoemulsions are prepared in a wide range of formulations, including foams, creams, sprays, and other kinds of cosmetic products.
- It shows higher drug penetration because the nano-sized particles can easily enter the rough skin surface and enhance bioavailability.
- It can be administered orally by using a biocompatible surfactant in a nanoemulsion formulation and is safe for transdermal application due to its non-toxic nature.

4.2 Disadvantages of nanoemulsion

- The stability of the nanoemulsion is influenced by temperature, pH and the Oswald ripening effect.
- Surfactants and cosurfactants are used in high concentrations to provide the desired stability (Paliwal *et al*., 2022).

5. Gel

Gels are an intermediate state of matter that has both liquid and solid components. Gel is a three-dimensional cross-linked system comprised of structural elements and an adequate volume of liquid that, when combined, creates an endlessly rigid network structure and immobilises the continuous phase of liquid inside. Organic macromolecules, mostly polymers or inorganic particles, can make up the structural components of the gel network (Saraswat *et al*., 2011). Chemical or physical interactions can result in the formation of cross-linkages. As a result, gels are divided into physical and chemical gel systems. Physical gels are formed by secondary intermolecular forces, which are relatively weaker, while chemical gels are associated with permanent covalent bonding (Larson, 1999).

5.1 Ideal properties of topical gel

- The gel should be clear, homogenous, non-sticky, stable, and inert in nature.
- When shear or force is applied while shaking the container, the gel should break easily.
- It should not cause any irritation to the skin.
- The viscosity should be optimal.
- The gel should never interact with other ingredients in the formulation.
- It should have antimicrobial activity (Samundre *et al*., 2020).

5.2 Advantages of gel formulations

- In comparison to other formulations, gels are simple to prepare.
- Gels have excellent adhesion to the application site.
- Gel is an elegant and non-greasy formulation.
- Have excellent stress tolerance.
- Gels are eco-friendly and biocompatible.

5.3 Disadvantages of gel formulation

- The gelators may cause irritation.
- The effect of gels is relatively sustained and slower.

- The presence of water increases the risk of a microbial or fungal attack on gel.
- In some gels, flocculation results in an unstable gel.
- Solvent loss from the formulation dries the gel (Jeganath and Jeevitha, 2019).

6. Nanoemulgel

The term "nanoemulgel" refers to a nanoemulsion that incorporates a gelling agent. In this case, an emulsion might become an emulgel due to the water content of the gel. Various marketed gel and emulgel products are given in Table 1. When emulsion droplets are smaller than 500 nm, droplet separation is far less likely than in a general emulsion (Kim *et al*., 2008). This gel-based nanoemulsion is a desirable nanolipoidal drug delivery through skin due to its great properties such as thixotropic behaviour, being greaseless, biocompatibility, being readily removable, easy spreadability, *etc*. (Anand *et al*., 2019).

When lipophilic drugs incorporated in hydrogel (gel) have less spreadability and permeability, the two systems-nanoemulsion and hydrogel, were combined to form nanoemulgel (Figure 1) (Eid *et al*., 2014), and the limitations could be solved. The drug is initially released from the inner phase to the outer phase, and then it travels to the skin's surface. When nanoemulgel is applied to the skin, nanosized oily droplets of gel matrix penetrate much deeper into the stratum corneum than other topicals (Sapra *et al*., 2013).

The high solubilization of the drug in the oil phase and the good adhesion properties of nanoemulgel result in a greater concentration gradient towards the skin and increased drug penetration (Malay *et al*., 2018). Different polymer components, surfactants, and fatty substances of natural, synthetic, and semi-synthetic origin are used in nanoemulgel (Aithal *et al*., 2020). The drug release in the nanoemulgel depends on the composition of a network of polymer chains, crosslink density, presence of surfactants, and penetration enhancers (Syamala, 2013).

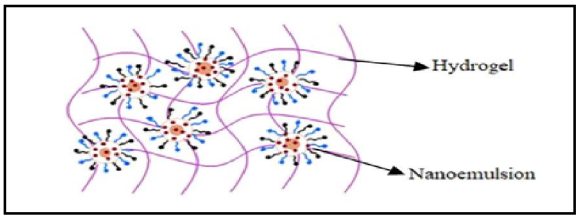

Figure 1: Structure of nanoemulgel.

6.1 Advantages of nanoemulgel

- Nanoemulgel is non-irritating and non-toxic.
- Increased drug solubility, deposition, and skin permeability
- Additionally, a strong concentration gradient produced by good skin adherence, spreadability, stability, and high solubilizing power increases drug penetration as it moves downward.
- Drug loading is better in comparison to other formulations.
- Drugs with a shorter half-life can be released under controlled conditions and produce a prolonged therapeutic effect (Joshi *et al*., 2011).

6.2 Components of nanoemulgel

Oily phase: Mineral oils such as coconut oil, olive oil, rose oil, clove oil, eucalyptus oil, and numerous fixed oils (maize oil, cottonseed oil) (Montenegro *et al*., 2006).

Aqueous phase: Distilled water is commonly used as the aqueous phase.

Surfactant and co-surfactant: Surfactants are used to provide emulsification at the time of formulation and maintain stability. The selection of surfactant depends on the type of emulsion (W/O or O/W) (Savale, 2015). For example, tween80, span80, TPGS, acrysol, stearic acid, labrasol, sodium stearate, where cosurfactants or cosolvents like transcutol, captex, *etc*.

Gelling agent: It provides the structural network needed to prepare gels. Natural polymers include tragacanth, agar, xanthan gum, and guar gum. Semisynthetic and synthetic polymers include carbapol, HPMC, and poloxamer.

Permeation enhancers: These substances interact with various skin constituents to enhance permeability through the following mechanisms:

- The highly compact structure of the stratum corneum (SC) is disrupted.
- Partition of drugs, solvents, or co-enhancers is improved in the SC.
- Intercellular protein interaction is the crucial step in creating an alternate polar route to cause conformational changes in proteins or solvent swelling. Some enhancers increase the protein's fluidity in SC, whereas others affect both routes by disrupting the multilaminate pathway (Mortazavi and Abou Fazeli, 2003). For example, eucalyptus oil, isopropyl myristate, lecithin, oleic acid, urea.

6.3 Preparation of nanoemulgel

A nanoemulsion can be prepared using high-energy or low-energy techniques. The low energy method includes phase transition, self-emulsification, phase inversion, and temperature approaches. Mechanical devices such as high-pressure homogenizers, microfluidizers, and ultrasonicators can be used in the high-energy method to provide a strong disruptive force to break the water and oil phases and produce nanosized droplets. Regardless of the techniques, there are three steps in the preparation of nanoemulgel (Figure 2).

Step 1: Formulation of the nanoemulsion: Drugs and emulsifiers are dissolved in the oil phase or aqueous phase, depending on the solubility of the drug. The aqueous and oil phases are heated; they are mixed by gradually adding one phase into the other, continuously stirring until at room temperature.

Step 2: Gel formulation: To make the gel base, adjust the pH while dissolving the appropriate polymer in purified water using a mechanical stirrer.

Step 3: Formulation of nanoemulgel: To incorporate the nanoemulsion into the gel system and gently mix it until to get a uniform nanoemulgel (Sengupta and Chatterjee, 2017).

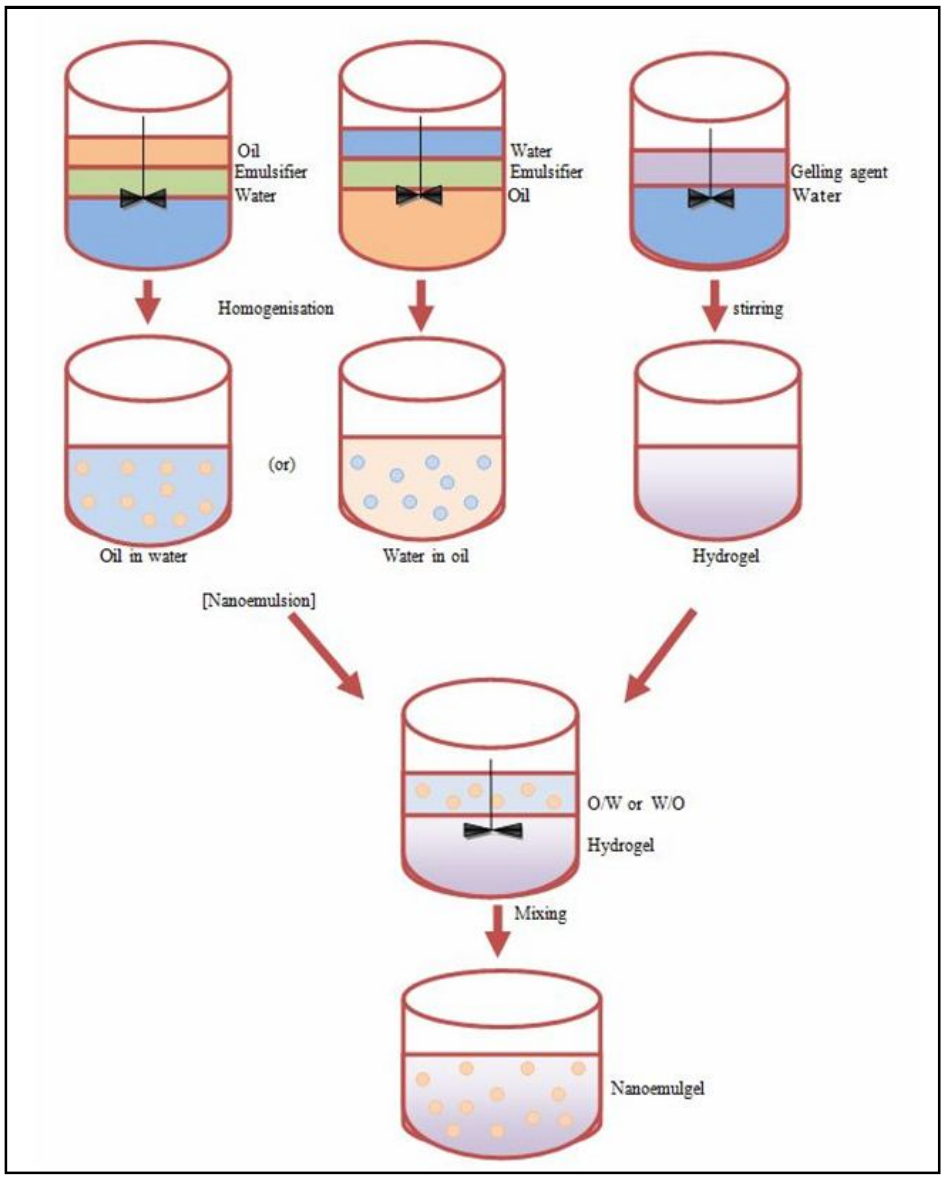

Figure 2: Schematic representation for the preparation of nanoemulgel.

6.4 Characterization of nanoemulgel

Visual examination: It could be visually examined to determine its colour, appearance, and homogeneity (Soliman *et al*., 2021).

pH evaluation: It is determined by using a digital pH meter (Basera *et al*., 2015).

Determination of viscosity: The viscosity of the gel is essential for efficient skin application. Viscosity is the measure of a fluid's resistance to flowing and a higher viscosity indicates a greater flow resistance. Viscosity is measured by using Brookfield's Viscometer.

Spreadability measurement: The spreadability of nanoemulgels is assessed using their "Slip" and "Drag" properties.

Measurement of droplet size and polydispersity index: To determine droplet size, the dynamic light scattering (DLS) method is used. According to the light scattering theory, the polydispersity index (PDI) measurement indicates droplet diameter and size distribution and is determined by scattered light intensity (Azeez and Alkotaji, 2021).

Zeta potential: Nanoemulgels containing gelling agents and nanoemulsions that exhibit an electrical charge due to the presence of different types of surface active agents may affect the stability of the formulation, as measured by Malvern Zetasizer® nano-ZS ZEN 3600, ZeeCom-2000, *etc*. (Anand *et al*., 2015).

Drug content: The total quantity of drug present in the formulations is determined by various analytical methods.

Accelerated stability study: According to International Council for Harmonisation (ICH) guidelines, the formulations are maintained for three months in an oven at 37 ± 2°C, 45 ± 2°C, and 60 ± 2°C. Every two weeks, the drug content is determined (Azeez and Alkotaji, 2021).

Skin irritation test: The preparation is applied to the well-shaved skin of a rat, and any negative effects, such as irritation, colour change in the skin, or morphology, should be observed for up to 24 h. The test is considered successful if no irritation occurs (Bhavesh and Shah, 2016).

***Ex vivo* drug permeation studies:** *Ex vivo* permeation studies were conducted using Franz diffusion cells. Excised skin from Wistar rats was used. The hair on the dorsal side of the slaughtered animal was removed from tail to head. The animal's skin was separated, washed with normal saline, and checked for integrity. 20 ml of phosphate buffer with a pH of 7.4 at 37 ± 5°C were placed in the receptor compartment of the diffusion cell and fixed on a magnetic stirrer that stirred at a speed of 100 rpm. The skin was attached to a diffusion cell assembly with an orifice size of 4.91 cm^2 and an effective diffusion area of 4.91 cm^2. Nanoemulgel is evenly applied on the surface of the skin, where it is in between the receptor and donor chambers. At appropriate intervals, an aliquot of the 2 ml sample was taken and analysed (Basera *et al*., 2015). To determine the quantity of drug diffused at a particular time interval, cumulative corrections are done. The aggregate quantity of drug that is diffused across the skin is determined as a function of time, and the drug diffusion kinetics were also calculated (Khurana *et al*., 2013).

6.5 Applications of nanoemulgel formulations

Nanoemulgel is an innovative topical delivery system with a variety of pharmacological actions. These impacts can be categorised as follows:

- Nanoemulgel is a promising alternative to other topicals for the treatment of pain and inflammation that have improved pharmacokinetic and pharmacodynamic action.
- For the treatment of psoriasis
- It produces antifungal activity for Candida infection in several folds when compared to other commercial emulgels.

Biocompatible polymers containing nanoemulgel produce a better therapeutic effect than traditional ophthalmic preparations for the treatment of ocular diseases (Anand *et al*., 2019).

Table 1: Available marketed products of gel and emulgel

Product name	Formulations	Uses	Manufacturer
Reumadep Emulgel©	Arnica, ashwagandha, myrrh, ginger, rosemary, cloves, mint	Anti-inflammatory and muscle relief	Erbozeta Energia Verde
Emulgel Levorag Monodose©	Liquorice, hibiscus, natural extract	Adjuvant for treatment of anal fissures	THD Lab Farmaceutici
Lord's Rheuma-Koll	Arnica montana, Cantharis, Gaultheria procumbans, Methyl salicylate	Joint pain and inflammation	Lord's Homoeopathic Laboratory Pvt. Ltd.
Rumalaya	Boswellia, gum resin, Indian winter green (*Gandhapura taila*) oil	Inflammations	Himalaya Wellness Company
Nature's essence	Aloe vera	Skin brightening	ESME Consumer Pvt. Ltd.
Heal plus	Curcuma longa, tea tree oil, cedar wood oil, and aloe vera	Burn and diabetic wounds	Sanat Products Ltd.

7. Discussion

The utilisation of plant-based therapies is growing in significance as people are drawn to natural approaches because of their wide range of medicinal qualities that can be utilised in many pathological and physiological health conditions. Raw plants and plant extracts include a variety of phytochemicals and bioactive substances that provide synergistic therapeutic effects and have various target effects to treat a wide range of diseases. These kinds of phytochemicals are frequently categorised as a pharmacological lineup for treatments for various diseases by lowering the risk of illnesses while promoting wellness (Fernando *et al*., 2022). These plant extracts have a wide range of biochemical properties, including anti-inflammatory, antidiabetic, antifungal, antimicrobial, and anti-cancer effects.

Traditional health medicines are being combined with modern pharmaceutical technology to increase their efficacy. In order to achieve greater efficacy from plant phytoconstituents, they must be delivered to the body by means of novel methods such as nanoemulgel and nanoemulsion. Researchers have become interested in converting nanoemulsions to nanoemulgels as they can counteract the low viscosity and spreadability problems of nanoemulsions. Due to the combined characteristics of nanoemulsion and gel base, nanoemulgel is considered to be the better choice for administering drugs to the skin (Bhavesh and Shah, 2016). The non-invasive route, better safety profile, high penetration ratio, ease of application, and spreadability nature of nanoemulgel have increased its therapeutic efficacy.

The availability of the largest surface area of skin of any other organ makes a topical drug delivery system a potential future trend for drug delivery. Although, the skin provides several benefits, such as ease of application, patient compliance, and safety, it also has many drawbacks, including permeability and bioavailability *via* first-pass metabolism, among others. Nanoemulgel can be a future trend for topical drug delivery due to its very small droplet size range, lipophilic character, and suitability for a wide range of administration routes, including topical, oral, intranasal, parenteral, ocular, and pulmonary. The oil, water, surfactants, co-surfactants, and gelling agents utilised for the formulation of nanoemulgel are relatively safe and nontoxic, making them suitable for human use

(Chaurasiya *et al*., 2021). Due to the compatibility of herbal drugs with nanoemulgel, it is regarded as the ideal technology for the green approach of the medicine system.

The development of a stable nanoemulsion and the conversion of nanoemulsion to nanoemulgel mainly depend on the primary methodology and the appropriate selection of its components. For transdermal delivery, it has been found that making hydrogel-thickened nanoemulgel from nanoemulsion is more effective and compatible (Sengupta and Chatterjee, 2017). Due to decreased interfacial tension and mobility of the dispersed phase, this viscous formulation may be more thermodynamically stable than nanoemulsion, which could lead to a more effective and efficient topical delivery system for pharmaceutical agents, particularly lipophilic phytomolecules, with the goal of enhancing skin permeation across the deeper layer of the skin due to the formation of a thin layer over the skin, improved contact time, and hydrating the skin **(**Choudhury *et al*., 2017).

Poorly water-soluble drug candidates that have been excluded from development processes due to limited clinical efficacy can be successfully delivered using nanoemulgel. The technique is believed to improve the pharmacodynamic and pharmacokinetic characteristics of drugs with low bioavailability, resulting in better patient compliance. With numerous benefits, it could be inferred that the nanoemulgel system can be a more effective and feasible drug delivery method for topical treatment to obtain better treatment strategies and greater patient compliance in the near future for patients who have difficulty with medications taken orally **(**Bhardwaj and Tiwari, 2021).

8. Conclusion

Plant-derived nanoemulgels have benefits in the cosmetic and pharmaceutical industries. Due to its enhanced pharmacokinetic profile, spreadability, less sticky nature, greater penetration capabilities, and higher therapeutic efficacy, topical nanoemulgel loaded with phytoconstituents can be considered a better alternative to traditional topical formulations. In conclusion, the nanoemulgel system has the potential to develop into a safe, efficient, and widely recognised topical delivery system for herbal as well as lipophilic drugs in the future.

Acknowledgements

The authors would like to thank the management of Nandha College of Pharmacy for their constant encouragement, support, and guidance in the preparation of this review article.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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Citation **Sanjana Anto, S. Tamizharasi, T. Prabha, G. Gocika, S. Punitha, J. Thirumaran, P. Amsa and R. Sumathi (2023). Nanoemulgel as an innovative platform for phytomolecules. Ann. Phytomed., 12(2):239-245. http://dx.doi.org/10.54085/ap.2023.12.2.28.**