Review Article

Herbal Nanoemulsion in Topical Drug Delivery and Skin Disorders: Green Approach

Abstract

A topical drug delivery system can be a future trend for drug delivery because of the availability of the largest surface area of skin than any other organ. Although the skin has some advantages such as ease of application, patient compliance, and safety, it has many disadvantages such as permeability and bioavailability via first-pass metabolism and others. Nanoemulsion can be a future trend for topical delivery of drugs because of its very fine droplet size range, lipophilic and/or hydrophilic nature, and suitability for various administration routes such as parenteral, oral, topical, intranasal, ocular, and pulmonary. The contents of nanoemulsions make them suitable for human use because the oil/lipid, water, surfactants, and co-surfactants used in the formulation of nanoemulsion are relatively safe and nontoxic. Nowadays, people are more attracted to natural preparations as of their inherited qualities and fewer side effects. Due to herbal drugs' compatibility in nanoemulsion, it is considered the best technology for the green approach of the medicine system. The article presented the foundation for the above statement by different literature surveys on the herbal nanoemulsion formulations.

Keywords: *Co-surfactant, greens, nanoemulsion, surfactant, topical delivery*

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Introduction

Human skin is a stratified epithelium, covering 1.6 m^2 of surface region and representing roughly 16% of a grown-up's body weight and consist of a different cell type that performs a distinct function. In direct contact with the outside condition, the skin assists with keeping up four basic body functions: (1) maintenance of dampness and counteraction of pervasion or loss of different molecules, (2) maintenance of body temperature, (3) assurance of the body from organisms and destructive outer impacts, and (4) sensation.[1]

The skin may be comprehensively partitioned into the outer epidermis, dermis, and undermost hypodermis [Figure 1]. In addition, the epidermis can be divided from outside to within into stratum corneum (horny layer), stratum granulosum (granular layer), stratum spinosum (prickle cell layer), and stratum basale (*Stratum germinativum*). The stratum basale and spinosum are considered known as the malpighian layer. The additional layer stratum lucidum can be seen on the part of the body with thickened skin example, the palm and bottom of the foot. The hair follicle and sweat glands cross different skin layers.[2]

Skin is the primary course of the topical drug delivery system. Skin disease affects the population and has been cited as one of the top 15 ailments for which prevalence and medical service expanded in the most recent decade.[4] Improvement in the biological sciences with an increasing dermatological market increases the advent of batter topical formulations. Topical drug delivery systems include a wide range of pharmaceutical dosage forms such as solid powders, semisolids, liquids, and sprays preparations. Gels, creams, and ointments are mostly used in semisolid preparation for topical drug delivery. There are the following advantages associated with topical drug delivery systems:[5]

- Patient acceptance and compliance,
- Ease of application,
- Noninvasive and painless method of administration,
- Improved drug bioavailability,
- Good pharmacological and physiological responses
- Minimum systemic toxicity
- Minimum exposure of the drug to non-infectious tissue sites.

In addition to the advantages elucidated here, the major challenge in topical delivery is the permeability of the drug across skin and

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bioavailability profile. Nanoemulsions have been developed to defeat debilitated drug permeation following the topical application as shown in Figure 2.[6,7]

In addition, as an emulsion, either o/w or w/o is scattering of two liquids that are immiscible, stabilized by using a suitable surface active agent, the nano suffixed for its mean droplet size radius achieved in normally less than 500 nm.[8,9]

Nanoemulsions may be formulated in a variety of delivery forms, such as oils, creams, sprays, gels, aerosols, foams, and may be administered uniformly through different routes, such as topical, dental, intravenous, intranasal, pulmonary, and ocular.[10,11]

Advantages of Nanoemulsions[12]

- Because of the nanosize and wide interfacial area of the droplets, there is an improvement in solubility, dissolution, absorption, permeation, and bioavailability.
- The physical stability of herbal bioactive can be improved by encapsulation into the nanoemulsion matrix.
- As oils/lipids are compatible with the body, quickly metabolized, and nontoxic, the nanoemulsions are safe for human health.
- Allows a targeted and sustained transfer of active molecules.
- Toxic effects of the drug can be minimized due to a reduction in dose and provide better therapeutic effects.

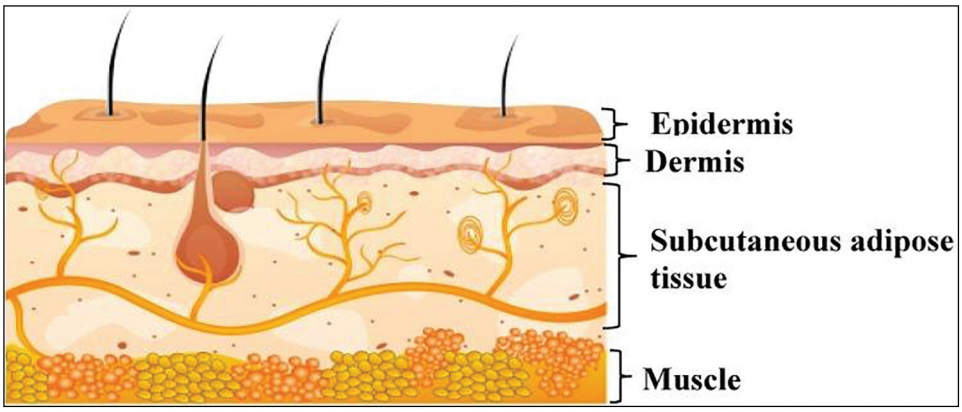

Figure 1: Structure of skin[3]

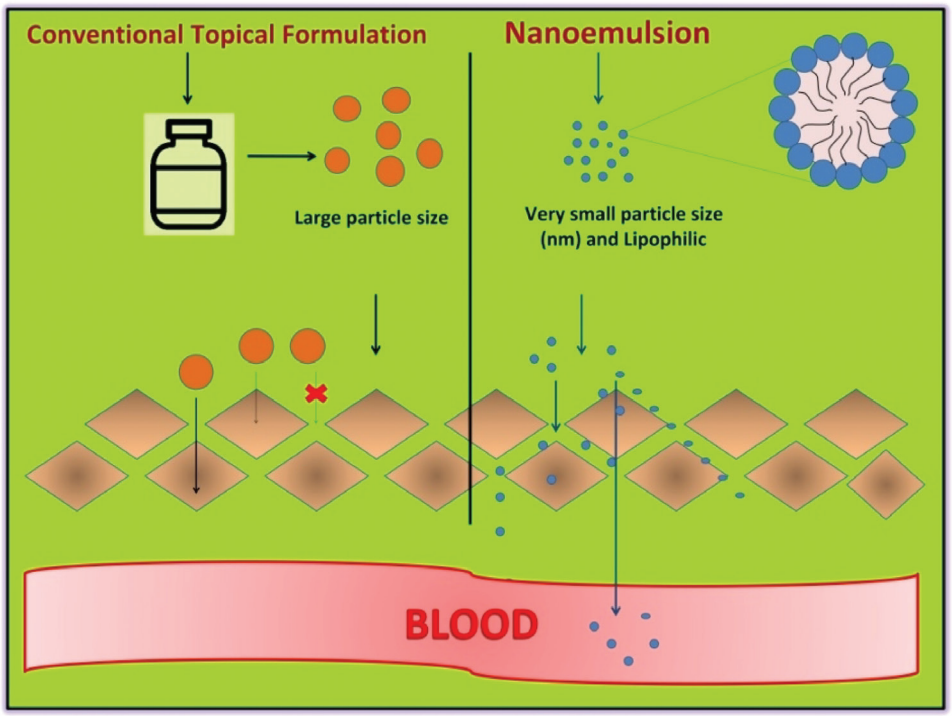

Figure 2: Topical absorption of conventional dosage form and nanoemulsion

- Due to their solubilization and transportation ability of both hydrophobic and hydrophilic active compounds with unusual physical properties, nanoemulsion has been the subject of extensive research globally.[13]
- It improves plasma drug concentration because it avoids first-pass metabolisms.
- Provides value-added nutraceutical and dietary supplement distribution system.
- Improve patient compliance.

Formulation of Nanoemulsion

1. *Oils:* O/W nanoemulsions consist of 5%–20% oil/lipid as disperse phase, even sometimes it may be more significant up to 70%. Lipids/oil used in nanoemulsions is usually based on the solubility of the drug.[14] It helps to facilitate emulsification to increase the solubility of the water-insoluble drug in the oil droplets. It also improves the absorption of the oral drug by increasing the gastrointestinal drug permeation through the intestinal lymphatic. For topical formulations, it functions as a penetration enhancer that facilitates drug permeation in the skin.[15,16]
2. *Surfactants:* Surfactants are the agent that minimizes the interfacial tension of oil and water and act as the emulsifier in the formulation of nanoemulsion. They rapidly adsorb on the oil and water interface and provides steric or electrostatic, or double electro-steric stability. HLB value plays an integral part in the selection of appropriate surfactants. 30–60% v/v concentration of surfactant is used to produce a stable emulsion.[17,18] Lecithin (phosphatidylcholine) is derived from egg yolk or soybean and is used as a common surfactant used in nanoemulsions.[19]
3. *Cosurfactants:* Cosurfactants are used to increase the effectiveness of surfactants. It should be used in smaller concentrations owing to its adverse side effects at greater concentrations.[20,21]
4. *Stabilizers:* Different kind of stabilizers is used to overcome the instability issues of nanoemulsion such as flocculation, coalescence, Ostwald ripening, and gravitational separation.[21] The contents of nanoemulsion are summarized in Figure 3.

Green Approach

The importance of herbal drugs and formulations is increased worldwide for all sorts of diseases. People are well aware of the ingredients, therapeutic and medicinal properties of the ingredients of their daily diet. Plants have a no. of very beneficial bioactive compounds, which work as a backbone of the conventional medicine system. Numerous sorts of diseases have been known to be treated with natural cures. This action is because of the presence of phytochemical components such as glycosides, tannins, alcohols, and aldehydes. People are attracted to the herbal medicine system because of its fewer side effects and low-toxicity profile.

Because of the quick staged way of life and polluted environment, individuals are presented with numerous ways of life, particularly skin diseases.[22]

Examples of few herbs that are effective in some diseases are given in Table 1.[21,22]

Importance of Nanoemulsion in Delivery of Herbal Drugs

- Either the most recent decades, it has become a pushed region of research for some specialists and trailblazers all through the world because of their medical advantages;

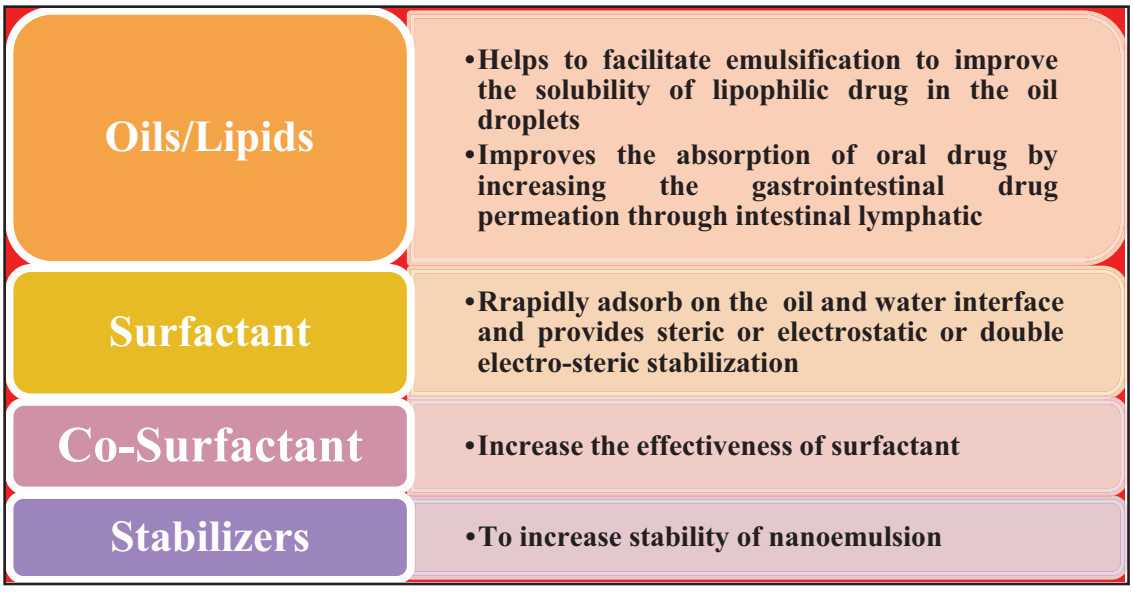

Figure 3: Contents of nanoemulsion

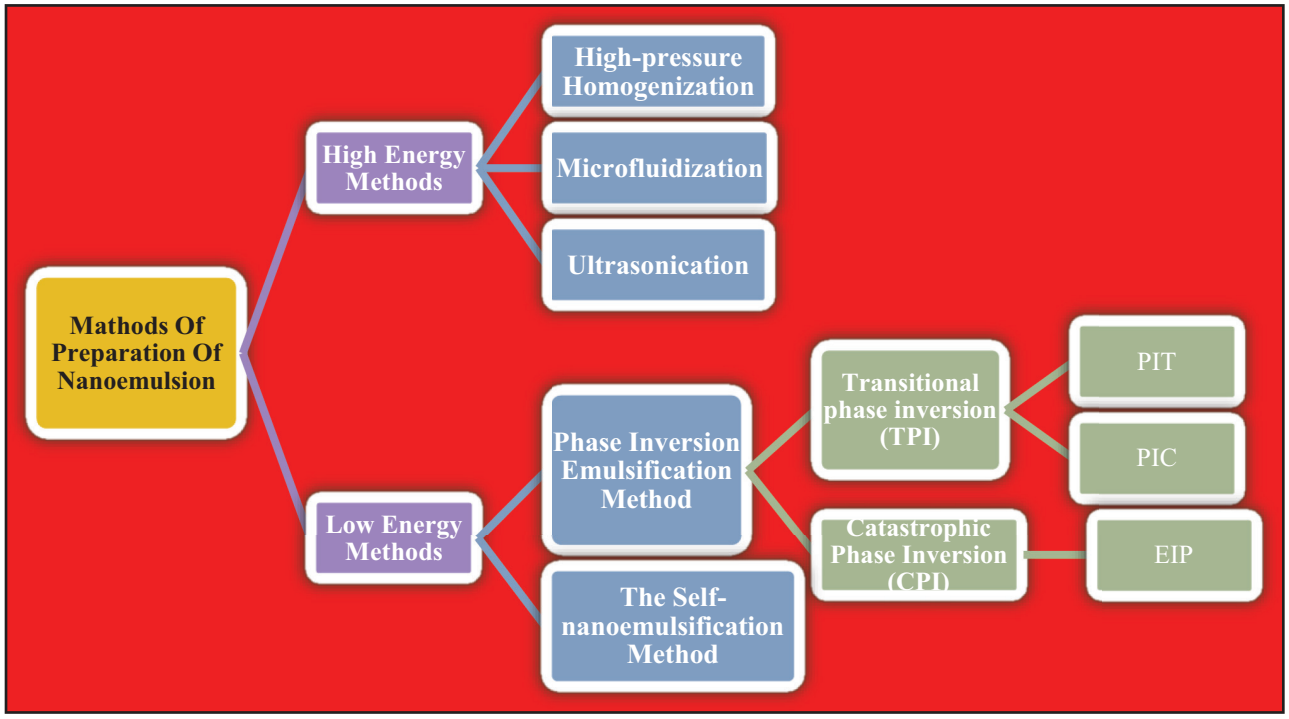

Figure 4: Methods of preparation of nanoemulsion

Table 1: Examples of therapeutically useful herbs

Common name	Botanical name/family	Parts used	Indications
Worm killer	*Aristolochia bracteolate, Aristolochiaceae*	Rhizome, root, seeds	Antitoxic, antiperiodic
The Bishops weed	*Carum copticum, Apiaceae*	Seeds	Cholera, indigestion cough
The round zeodary	*Curcumaaromatica, Zingiberaceae*	Rhizome	APD, skin wound
Tellicherry bark	*Holarrhenapubescens, Apocynaceae*	Bark	Diabetes, dysentery
Ivy gourd	*Coccinia grandis Cucurbitaceae*	Fruit, leaf, rhizome	Ulcers in the tongue, diabetes, skin disorders
True Indigo	*Indigoferaspalathoides, Fabaceae*	Root	Dental problems
Black cumin	*Nigella sativa, Ranunculaceae*	Seed	Rhinitis aphrodisiac
China root	*Smilax china, Smilacaceae*	Bark	Leucorrhea indigestion, diabetes
Sweet obtuse leaved mimusops	*Wattakaka volubilis, Asclepiadaceae*	Fruit	Antidote febrifuge
Indian beech	*Pongamia pinnata, Fabaceae*	Flower, root, seed, leaf	Ulcers anemia leucorrhea indigestion
Indian bdellium tree	*Commiphora myrrha, Burseraceae*	Whole plant	Amenorrhea anemia
Indian mulberry	*Morinda tinctorial, Rubiaceae*	Root bark	APD, pharyngitis
Snakewood	*Strychnosnuxvomica, Loganiaceae*	Seeds	Nervine disorders, uterine fibromas, epilepsy
The Portia tree	*Thespesiapopulnea, Malvaceae*	Bark flower seeds	Anti-inflammatory, vitiligo ascites
Balloon plant	*Cardiospermum halicacabum, Sapindaceae*	Leaf root	Chronic cough, amenorrhea

however, the pharmaceutical use of natural bioactive and phytopharmaceuticals is restricted with low solubility, permeability, and bioavailability. It has become the most significant obstacle for the effective use of natural bioactive against different health complications. These hurdles can be solved with the formulation of nanoemulsion of herbal drugs.[23] Nanoemulsion is considered the best technology because of its:[24]

- Damp or smooth behavior,
- Eminent interaction with the skin cells,
- Small droplet dimension,
- Efficient permeability,
- Protection
- Capability to convey volatile, irritant, and high molecular weight drugs evenly.
- Nanoemulsions easily associate with the skin cells due to their fluidic behavior and emulsifier properties at the interface.
- Nanoemulsion leads to provide better efficacy and interaction due to surface charge over nanoemulsion.

Formulation and Development of Herbal Nanoemulsion

Prior to the production of a quality nanoemulsion product, it is necessary to note the choice of ingredients, their correct concentration, an order of addition, proper preparation method, optimum stirring speed, and shear stress. There are several techniques that are used for the preparation of nanoemulsion [Figure 4]:[25]

High-Energy Methods

The method is called high energy because it uses high mechanical energy using no mechanical devices such as ultrasonicators, microfluidizers, and high-pressure homogenizers to provide strong disruptive forces, which breaks large size droplets into nanosized droplets and produce nanoemulsions with high kinetic energy.[26,27] High-energy methods provide better control of particle size with a choice of formulation composition, stability, rheology, and color of the emulsion.[28] High-energy methods contain a no of methods that are given below.

High-pressure homogenization

High-pressure homogenization creates intense turbulence and shear flow to the nanoemulsion mixture under very high pressure, resulting in the breakage of the dispersed phase into small droplets, that is, less than 100–1 nm. The relative flux between the droplets governs the dynamic equilibrium between breakage and coalescence, due to which homogenous droplets with better shelf life and texture characteristics are produced.[29]

Microfluidization

Microfluidization is a high-pressure homogenization technique used to develop a highly dispersed system. A microfluidizer co-existently uses hydraulic shear, impact, attrition, impingement, intense turbulence, and cavitation for effective size reduction. It forces feed material through an interaction chamber consisting of microchannels under the influence of a high-pressure displacement pump (500–50,000 psi), which results in the formation of very fine droplets.[30,31] Precarious and finest nanoemulsion particles are produced in microfluidizers than homogenizers and produce stable nanoemulsions at low surfactant concentrations.[32,33]

Ultrasonication

Ultrasonicator is used in this method to convert macroemulsion into nanoemulsion. Ultrasonicator is consists of a probe that emits ultrasonic waves. The desired particle size and stability of nanoemulsion is achieved by varying ultrasonic energy input and time. In ultrasonication, the acoustic cavitation process is used to provide physical shear. Cavitation is a process of the development and growth of microbubbles, accompanied by the collapsing of microbubbles, caused by pressure changes in the acoustic wave. The formation of nanosized droplets results from the intense turbulence caused by the collapse of microbubbles.[34,35]

Low-Energy Methods

Low-energy emulsification methods use the system's intrinsic chemical energy and require delicate mixing for the preparation of the nanoemulsions.[36,37]

Phase inversion emulsification method

spontaneous surfactant curvature occurs by changes in variables such as temperature and composition induces phase transition in the process of emulsification.[38] Phase inversion emulsification methods are of two types: transitional phase inversion (TPI) methods, which involve phase inversion temperature (PIT) method and phase inversion composition (PIC), and continuous phase inversion (CPI) methods, which involve emulsion inversion point (EIP).

TPI happens due to the changes in random curvature or orientation of the surfactant due to variation in the variables such as temperature and composition.[39,40] However, CPI occurs when the scattered phase is gradually inserted as the scattered phase droplets are collated together to create bicontinuous/lamellar structural phases.[36] In the PIT method, the curvature of the surfactant is reversed by altering temperature. The PIC method is identical to the PIT method; however, in PIC, inversion is accomplished by adjusting the system composition instead of the system temperature.[37] In PIC, one element such as water is introduced to the mixture, and oil/lipid -surfactant or oil/lipid is added to the water-surfactant mixture. In the EIP method, phase inversion occurs through CPI mechanisms. The catastrophic phase inversion is caused due to change in the fractioned volume of the dispersed phase instead of the properties of the surfactant.[38]

Self-nanoemulsification method

Formation of nanoemulsion formation without changing the spontaneous curvature of the surfactant is achieved in the self-emulsification method. Surface active agents and/or co-solvent molecules are quickly diffuse from the scattered phase to the continuous phase, which triggers turbulence and generates nanosized emulsion droplets.[35,36]

Successful Topical Herbal Nanoemulsion Formulations

With the help of literature, numbers of successful herbal nanoemulsion formulations were found and presented, as shown in Table 2.

Conclusion

With a number of skin functions, there are a few significant challenges in drug delivery through the topical route. Nanoemulsion defeats these limitations and is found to be one of the best formulations for topical drug delivery, and nanoemulsion can also be formulated in a variety of delivery forms. In the era of allopathic medicines, people are attracted to green approaches because of varying and favorable qualities to use in many pathological and physiological

Table 2: Successful topical herbal nanoemulsion formulations

Drug	Uses	Polymer	Method	Results and output
Virgin coconut oil, green tea seed oil,	Relieve skin irritation and eczema anti-inflammatory, antiaging,	Soy lecithin, whey protein isolate, tea saponin, Tween 80	Ultrasonication techniques	Tea saponin natural emulsifier produced smaller size nanoemulsion than Soy lecithin compared to isolated whey protein due to steric and electrostatic repulsion and augment in surface area than and provided higher bioavailability.[41]
Cumin seed oil	Topical antibacterial	Tween 80	Ultrasonication technology	Because of its favorable oil-in-water (O/W) characteristics the cumin nanoemulsion was formulated with the nonionic surfactant. Tween 80 show efficient solubility and also reduce droplet diameter effectively by adhering to the droplet surface, enhancing the overall stability of the O/W emulsion system.[42]
Mangostin extract, virgin coconut oil	Antimicrobial	Span 20, Tween 20	Ultrasonication technology	Mangostin extracts loaded nanoemulgels showed high release of bioactive mangostinpolyphenol than its emulgel and investigated significant antimicrobial activity against *S. aureus* and *E.coli*because.[43]
Satureja montana L. essential oils	Antioxidant, anti-inflammatory	Tween-20, Tween-80	Sonication	Appropriate mixing of SEOs and surfactants permitted the formation of O/W nanoemulsions with a droplet hydrodynamic diameter in the nanometric range, verified by DLS and TEM analyses and Negative ζ-Potential capable of ensuring high storage stability of the nanoformulations proposed.[44]
Garlic oil	Antifungal, antimicrobial	Tween 80, Span 80, potato dextrose agar (PDA), potato dextrose broth	Ultrasonication	By formulating nanoemulsion of garlic oil, the bioavailability of garlic oil has been increased by almost 300 considerations of stability, antifungal activity, and mean particle size.[45]
Curcumin	Antimicrobial, antioxidant, anti-inflammatory	Non-ionic surfactant	Both low-energy and high-energy methods	Accessible research study suggest that over six nanoemulsions formulation Techniques were used to encapsulate curcumin, namely low-energy method (PIT and PIC), high-energy method (HPH, microfluidization, and ultrasonication) and intermediate energy method (membrane emulsification).[46]
Fish oil	Antioxidant, kidney related problems	Tween 20, soybean protein isolate-phosphatidylcholine	Ultra-high pressure homogenization	Study compares fish oil nanoemulsion containing tween-20 and SPI-PC and find that between 20 nanoemulsions, SPI-PC nanoemulsions have improved storage stability, oil oxidation stability, and Na+ resistance due to higher SPI / PC surface load density.[47]
Rutin	Antiviral, antioxidant, anti-inflammatory	Tocopheryl polyethylene glycol 1000 succinate, sefsol 218, Solutol HS15, Transcutol P	High-pressure homogenization	It can be inferred that rutin nanoemulsions have been effectively prepared and may serve as an efficient method for improving oral bioavailability and efficacy of rutin. The pharmacokinetic tests have shown a double increase in oral bioavailability.[48]

Table 2: Continued

Drug	Uses	Polymer	Method	Results and output
Aliskiren hemi-fumarate	Antihypertensive	Capryol 90, Labrafil M1944 CS, Transcutol HP, Isopropyl myristate, Tween 80, Tween 20, olive oil, polyethylene glycol 400, Cremophor® RH 40	Sonication	The Cmax and AUC0 of SNES formulations were 25 & 3.05 and 2.5 fold rises and greater drug permeation compared to drug solution.[49]
Araucaria heterophylla resin	Antiviral, anti-inflammatory	Tween 80	Ultrasonication	Essential oil nanoemulsion A. Heterophyll resin shows strong antiinflammatory and antipyretic activity *in vivo*, in addition EO of A. Heterophyll reduced inflammatory cytokine production.[50]
Brazilian red propolis benzophenones-rich extract	Antimicrobial	Egg-lecithin, medium chain triglycerides, DOTAP	Spontaneous emulsification procedure	This article is pointing to the high antifungal potential of nanoemulsion formulations involving natural products derived from BRP and can be deemed a promising option for the topical treatment of NAC-infection.[51]
Polyphenon 60 Cranberry Curcumin	Antibacterial antibacterial, diuretic antibacterial, antioxidant	Oleic acid, soyabean oil, Tween 20, glycerol, polyethylene glycol	Homogenization and ultrasonication techniques	Nanoemulsions of polyphenon 60, cranberry, and curcumin were prepared to improve the antibacterial potential and study the mechanism of antibacterial action of the encapsulated compounds.[52]
Hempseed oil	Anti-inflammatory	Lecithin, pea proteins	Ultrasonication	Reflect the possibility of using lecithin-based water/oil emulsions as a stabilizer for hempseed oil (HSO) with lecithin as a co-surfactant. Despite the strong stability of the prepared nanoemulsion, these can potentially be used in biomedical and cosmetic applications.[53]
Curcumin	Antimicrobial, anti-inflammatory, antioxidant	Lecithin, Labrasol, Transcutol HP Ceteth 10	Spontaneous emulsification method	A 28-fold increase in permeation of curcumin loaded nanoemulsion in comparison to ethanol-water based because limonene terpene enhances the skin diffusivity.[54]
Limonene	Essential oil, antioxidant, anti-inflammatory	Soya lecithin	Ultrasonication	Adding the antimicrobial to the Nanoemulsion, generated under isothermal heating conditions make it possible to reduce the therapy period by a factor of 25 using a revolutionary approach using soy lecithin, a natural compound as well as essential oil. It can increase quality of the product without affecting its safety.[55]
Thyme oil, lemongrass oil, cinnamon oil, peppermint oil clove oil	Antibacterial, antifungal anti-inflammatory stiffness in the muscle and joints, nourish the skin, antiaging, calm dry skin antiseptic, antibacterial antimicrobial	Tween 80	Microfludization	Five physically stable essential oils nanoemulsions were formulated. The type of essential oil and their concentration were found to have a phenomenal influence on the antifungal activity of mycelia growth.[56]
Clove oil	Antimicrobial, antiaging	Tween 80, eugenol, eugenol acetate, caryophyllene	Homogenization	Barley treated with a greater concentration of nanoemulsion clove oil had less germinating capacity. All clove oil nanoemulsions were capable of inhibiting fungal growth and development of DON during the micromalting process.[57]

Table 2: Continued

Drug	Uses	Polymer	Method	Results and output
Quercetin	Antiarthritic, anticancer	Oleic acid, arachis oil, castor oil, sesame oil, coconut oil, soy oil, olive oil, sunflower oil, isopropyl myristate (IPM), Tween 20 (Polysorbate-20), Polyethylene glycol-400 (PEG-400), Propylene glycol, Transcutol P Cremophor RH 40, Capryol 90, Carbopol 940	Vortex mixing	Nanoemulsion of quercetin was formulated with the incorporation of Oleic acid: Arachis oil, Tween 20 and PEG-400 (15:6:6) as a successful carrier system to overcome the drawback of limited bioavailability from the topical route because of low skin permeability.[58]
Astaxanthin Alpha-tocopherol	Anti-Alzheimer, Anti-Parkinson antioxidant	K-carrageenan, sodium caseinate, polyethylene glycol, Span® 80, Tween® 80, sodium azide, medium-chain triglyceride oil,	Ultrasonication	In a shorter period, NEs has acted as an economically viable potential therapeutic option for diabetic wounds with the high operation.[59]
Thyme oil	Antibacterial, antifungal	Quillaja saponin, Soy lysolecithin, BSA	High-pressure homogenization	Thyme oil immersed in nanoemulsion droplets showed an increased inhibitory behavior of mycotoxin relative to bulk thyme oil.[60]
Duck oil	Improve vascular function	Medium-chain triglyceride oil, Soy lecithin, Tween-80	Ultrasonication	The duck oil nanoemulsion suppresses Ang II mediated senescence of VSMCs by increasing transcription of SIRT1and the anti-aging activity of duck oil in vascular systems facilitate the possible use of this oil as a therapeutic food to boost vascular function.[61]
Cinnamon oil	Stiffness in the muscle and joints, nourish the skin, antiaging,	Usnic acid, linseed oil, oleic acid, isopropyl palmitate, arachis oil, light liquid paraffin, isopropyl myristate, ethyl oleate, Tween 80, Span 20, Tween 20, Span 80, propylene glycol and poly ethylene glycol 400	Ultrasonication	Avoidance of disease progression by natural occurring antioxidant compounds nanoemulsion such as cinnamon oil and usnic acid have been shown to be an important technique for prophylaxis of DMBA / croton oil induced skin carcinogenesis.[62]
Eucommia ulmoides seed oil	Cardiovascular diseases	Tween 80	Dynamic high-pressure microfluidization	DHPM was a fairly easy and convenient technique for the processing of Eucommia ulmoid seed o/w nanoemulsions.[63]
Curcumin, eucalyptol,	Antimicrobial vascular diseases	Pinene Polysorbate 80, Soybean lecithin, Miglyol 812	Spontaneous emulsification method	The research connects microstructural properties to biopharmaceutical efficiency of monoterpene low-energy nanoemulsions for enhanced dermal curcumin distribution.[64]
Capsaicin	Local analgesic	Olive oil, Tween 80, Span 80, Carbopol® 934, Carrageenan	Spontaneous emulsification method	Preparation significantly decreased inflammation of rats with paw edema compared to the commercial cream and control group, particularly in the second and third hours of the study. Also, pretreated rats with capsaicin nanoemulsion gel showed very high pain resistance due to heat stimuli.[65,66]
Centella asiatica, *Lycopersicon esculentum Mil*., *Moringa oleifera Lam*. extract	Skin diseases	Virgin coconut oil, tween 80	High shear homogenization	High shear homogenization parameters are very critical considerations for regulating the properties of nanoemulsion such as particle size, PDI, zeta potential, and physical stability.[67]

Table 2: Continued

Drug	Uses	Polymer	Method	Results and output
De microalga spirulina lipid	Antioxidant	Tween 80	Ultrasonication	Nanoemulsions prepared without surfactant showed the ability of Spirulina sp. LEB18 microalgae in manufacturing biosurfactants, which is important because most of the surfactants used in factories are produced from petroleum, and there is growing interest in less violent microbial surfactant products.[68]
Phytol	Antioxidant	Tween-80, soy phosphatidylcholine, sodium oleate	Phase inversion method	Nanoemulsion of phytol decreases its side effects due to increase bioavailability and decreased dose.[69]

health conditions. The study results and exemplifies that an herbal drug's nanoemulsions can become the future fashion for both therapeutic and non-therapeutic applications.

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Conflicts of interest

There are no conflicts of interest.

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