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# ESSENTIAL OIL BASED NANOEMULSION FOR THERAPEUTIC APPLICATION- A REVIEW

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## ABSTRACT

Essential oil (EO) based nanoemulsion (NE) represent an emerging and promising approach in nanotechnology, serving as a safe and effective delivery system. Recent studies show that essential oils are one of the naturally occurring and eco-friendly approach which has broad spectrum of antioxidant and antimicrobial properties. EO can inhibit and/or kill many microbe species such as bacteria, viruses, fungi and other parasites. In this review, attempt has been made to use two essential oils from clove bud and lemon peel respectively to utilize their phytochemical constituents namely eugenol, limonenealong with few other bioactive components. Amongst various methods of EO extraction which includes steam, cold pressing, simple distillation and hydro-distillation; the last one is more preferred.This review discusses various methods of NE preparation, with particular emphasis on low-energy, spontaneous emulsification techniques and their advantages over high-energy methods.NE typically exhibit droplet size in the range of 20-500 nm which significantly offers improved stability, increases solubility, and enhances bioavailability for their higher surface area. The incorporation of EOs like clove bud and lemon peel oil enhances the potential of NE for their rich phytochemical compositions and biological activity. In addition, it focuses onthe evaluation and characterization parameters, which consist of droplet size, PDI, pH, zeta potential, morphology, thermodynamic stability, phase separation for stability of EO based NE and its antioxidant, antimicrobial activity for bioavailability. Their small droplet size makes them more effective for topical delivery by promoting interaction with the skin surface

and enhancing permeation across the skin barrier. NE is mostly utilized in food industry and aromatherapy, for their characteristic flavor and aroma, as well as in the cosmetics and pharmaceutical industry for their wide range of biological and therapeutic activities.

**KEYWORD**: Essential oil, Nanoemulsion, Hydro-distillation andLow-energy method.

## INTRODUCTION

Over the past decades, microorganisms have been recognized as one of the most significant and persistent challenges to public health worldwide. Microorganisms like bacteria, virus, fungi, and other parasites are naturally present on food, water, air and other surfaces. Such microbial contaminationraise questions about public health, food safety, and thereby healthcare environment. Under suitable conditions, these microorganisms grow rapidly causing spoilage and increase the risk of infectious diseases.[1,2] According to World Health Organisation (WHO), antimicrobial resistance (AMR) has reached unprecedented levels and conventional antimicrobial treatment is becoming less effective.[3] This warrants the need for effective antimicrobial strategies and proper hygienic practices to control microbial growth and prevent the spread of diseases.

Recent studies show that essential oils are the one of the naturally occurring and eco-friendly approach which has broad spectrum of antioxidant and antimicrobial properties. Essential oils (EOs) are aromatic, volatile compounds present in fruits, bark, seeds, pulp, peel, root and in the whole plant as well. Such EOs are secondary plant metabolites. These EOs composed of important phytochemicalslike polyphenols, flavonoids, terpenes, monoterpenes, sesquiterpenes, terpenoids, esters, alcohols, acids, aldehydes, aromatic hydrocarbons and ketone which make them unique and different from each other.[3,4]

As per study reports, EOs derived from plant parts of eucalyptus, thyme, clove, lavender, cinnamon, tea tree, ginger, oregano, orange, lemon, menthe, lemongrass, turmeric, rosemary, etc. contains bioactive components such as thymol, carvacrol, eugenol, citral, cinnamaldehyde, carvacrol, linalool, terpinen, menthol, limonene etc. These components are responsible for antimicrobial, antioxidant, antifungal, anti-inflammatory and other bioactive and therapeutic properties.[3,4] Citrus fruits including orange, lemon, citron, clementine and pomelo are particularly rich in limonene and other bioactive phytochemicals such as limonoids, flavonoids, carotenoids and terpenes.[5] Citrus fruit peel is an abundant source of EOs. It is reported that citrus EO exhibit moderate to high antibacterial and antimicrobial

activities.[4] Clove oil contains eugenol as major component. In addition, it also contains caryophyllene, eugenyl acetate, benzaldeyde, humulene, phenolic and sesquiterpene compound etc. as bioactive compounds. Such compounds exhibit analgesic, antimicrobial, antifungal and anti-inflammatory activities.[6] The incorporation of EOs like clove bud and lemon peel oil enhances the potential of NE for their rich phytochemical compositions and biological activity.Amongst various methods of EO extraction which includes steam, cold pressing, simple distillation and hydro-distillation; the last one is more preferred.[3,5]

However, the direct use of EO is often limited by their inherent characters such as high volatility, water insolubility, larger particle size, uncontrolled release at the site of application. Further, direct skin exposure may also lead to allergic reaction. To overcome these limitations, advanced delivery approaches such as microemulsion and nanoemulsion formulations have been explored for the transportation of drug through the skin. Such formulations are thermodynamically stable wherein the internal phase oil globules are of colloidal size range. As a whole, such systems show better therapeutic effectiveness.[7] This review is an attempt to describe the extraction process of essential oils, methods of NE development; evaluation of such formulation along with its applications.

**Nanoemulsion**

Nanoemulsions are increasingly being explored as effective carriers or vehicles for essential oils and drug delivery system. NE is a thermodynamically stable dispersion of oil and water stabilized by surfactant-co-surfactant mixture. An EO containing NE is a delivery system in which EOs are dispersed as very small droplets of colloidal size range typically ranging from 20 to 500 nm. NE consists of an oil phase, an aqueous phase, a surfactant and in many cases, a co-surfactant. They are classified based on their dispersion type: Oil-in-Water (O/W), Water-in-Oil (W/O) and Bicontinuous NE system. NE has huge potential compared to the conventional systems. NE enhances the solubility, stability, and bioavailability for both hydrophilic and lipophilic compounds. They are ideal for tropical or transdermal delivery due to their enhanced skin permeability.[6,8]

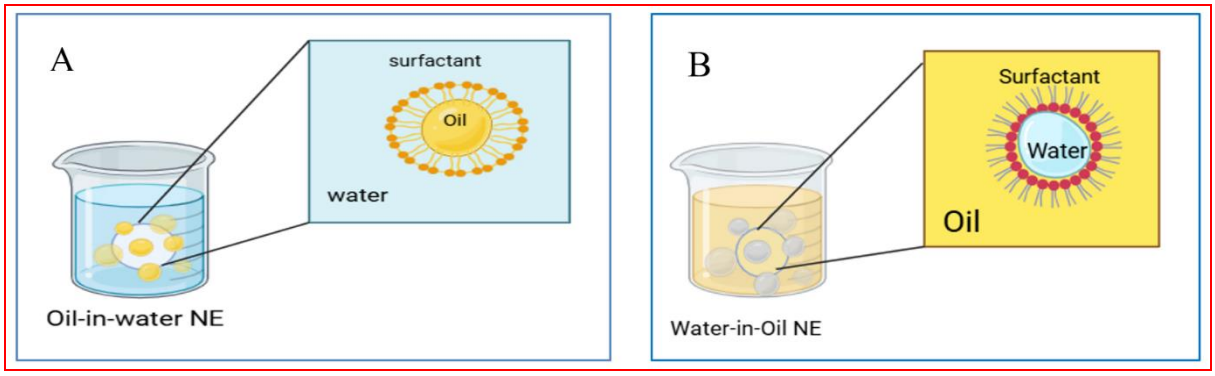


**Fig 1: Nanoemulsion, A. oil-in-water NE, B. water-in-oil NE.**

**Selection of compounds**

| **Essential Oils (with antimicrobial activity)**[3,5] | **Surfactants**[9,10] | **Co-surfactants**[9,10] |
|---|---|---|
| Eucalyptus, thyme, clove, lavender, cinnamon, tea tree, ginger, oregano, orange, lemon, menthe, lemongrass, turmeric, rosemary, | Tween 20, Tween 40, Tween 80, PEG 300, poloxy 60,Cween 80 polysorbate 80, polysorbate 20, span 20, span 80, span 40, | Ethanol, glycerine, PEG 400, polyene glycol, glycerol |

**Extraction of lemon and clove essential oil**

There are different techniques used for the extraction of EOs. These includes steam, cold pressing, simple distillation and hydro-distillation.[3,5] Studies show that steam-distillation and hydro-distillations are mostly preferred techniques as they are simple, efficient, cost-effective and easy to set up at laboratory scale. By comparing the results it is found that hydro-distillation yields higher essential oil than steam distillation.[11] Soxhlet extraction method resulted in higher yields in terms of quantity but lower quality due to low number of oxygenated compounds than that obtained from hydro-distillation using the Clevenger method.[12] The hydro-distillation method is a mixture of immiscible liquids, such as essential oil and water which is separated from each other. There are numerous separation techniques such as gravity sedimentation and liquid-liquid extraction.[11] It is found that combination of hydro-distillation using Clevenger apparatus with gravity separation is more effective than any other method.[11,12]

**Lemon peel essential oil** *(Citrus limon)***:** Fresh lemon peels were collected and then crushed to reduce their size. The essential oil was isolated by using hydro-distillation technique through Clevenger apparatus. Small pieces of lemon peels were placed in 1000 ml round bottom flask and distilled water was added to it. The mixture was heated for about 2 hours. During this process, the essential oil from the peel evaporates along with the water vapour

and vapour is then condensed and collected in a receiver. The collected liquid is a mixture of essential oil and water from which essential oil was separated.[13]

**Clove bud essential oil** *(Syzygiumaromaticum)***:** The essential oil was isolated by using hydro-distillation technique through Clevenger apparatus. Dried clove buds were placed in to 1000 ml round bottom flask and distilled water was added to it. The mixture was gently heated for about 2 hours. During this process, the essential oil from the buds evaporates along with water vapour and vapour is then condensed and collected in a receiver. The collected liquid is a mixture of essential oil and water, from which essential oil was separated.,[11]

**Methods of nanoemulsion Preparation**

They can be prepared using different methods including high-energy and low-energy techniques. The high-energy methods are high-pressure homogenization, micro-fluidization, and ultrasonication; on the other hand, low-energy methods are spontaneous emulsification, phase-inversion temperature and phase-inversion composition. In comparison, the low-energy method is more preferred as they requires less energy, simple and cost-effective for large scale production and also prevents the destruction of delicate molecules.[6,8]

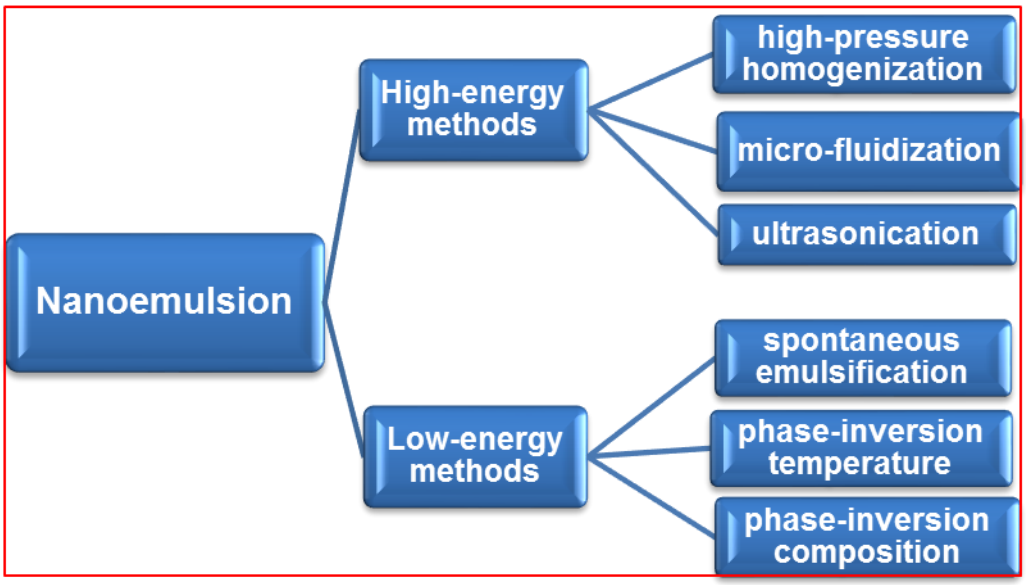


**Fig 2: Flow chart of method of preparation.**

**Low-energy, Spontaneous emulsification methods**

In the first step, the oil phase was prepared by mixing the selected oil with surfactants. The mixture was gently and constantly stirred using a magnetic stirrer for about 5-6 min. Then distilled water was added drop-by-drop to the mixture with continuous stirring. At a certain

point, clear, transparent and low viscous water-in-oil (W/O) NE was formed. This method is simple, cheaper, and easier to scale up and is best for delivering water-soluble drugs [6,8]. Shown in [Fig 3]

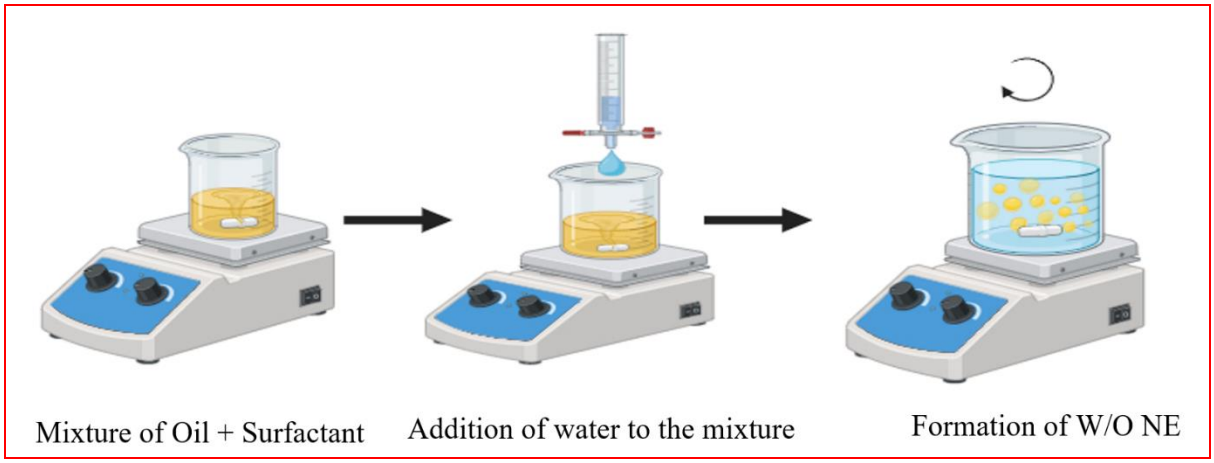


**Fig 3: Low-energy, Spontaneous emulsification methods.**

**Evaluations and characteristics parameters for Nanoemulsion.[3,7,14,15,16,17]**

| Name of the test | Determination | Apparatus | Ranges |
|---|---|---|---|
| **Physicochemical Characterization** | | | |
| Droplet size & size distribution | measurement of particle size and their distribution | Zeta sizer through Dynamic light scattering (DLS) | Optimal nano-emulsion size 20-200 nm[14] |
| Polydispersity index (PDI) | mean droplet size and indicates the uniformity in size of droplet | Dynamic light scattering (DLS)or Laser Diffraction and Photon Correlation Spectroscopy | PDI close to 0, indicates high homogeneity and stability in NE[14] |
| Zeta Potential or droplet surface charge | Measures the surface charges or net charges in the NE | Zeta sizer | Zeta potential values above ±30 mV indicates high stability due to strong electrostatic repulsion which prevents droplet aggregation.[14] |
| pH | Measures the pH of the NE | pH meter | It is to ensure skin and Pharmaceuticals compatibility pH4-8 is most preferable[14] |
| Morphology | Visualization the particle | Transmission Electron | - |

| | | | |
|---|---|---|---|
| | shapes and aggregation among the particles and shows 2D cross- sectional, 3D view of NE | Microscope (TEM) (2D view), Scanning Electron Microscope (SEM) (3D view) | [14,15] |
| Viscosity | Determine the viscosity of the fluid and measures the liquid resistance and type of emulsion. | Brookfield viscometer,Rheometers, Ostwald viscometer,Hoepplerfalling ball viscometer, Stormer viscometer, Menter (Haake Rotovisco), and Ferranti-Shirley viscometer | Low viscosity indicates o/w emulsion and higher viscosity indicates w/o emulsion.[15] |
| **Optical and Physical Characterization** | | | |
| Electrical Conductivity test | Detects the type of NE such as o/w or w/o | Conductometer | If bulb lights, it means o/w emulsion and if not then w/o emulsion.[15] |
| Optical Transparency | Measures percent transmittance. | UV-Visible Spectrophotometer | High transmittance approaching 100% indicates a transparent or translucent nanoemulsion.[15] |
| Phase separation | Visually observe clarity and separation of two separate layer (oil phase /water phase) or formation of creaming, and cracking. | Phase separation test | No phase separation indicate stability of NE.[14] |
| Refractive Index (RI) | Asses the optical clarity of NE and compared with water. | Abbe - Refractometer | If RI of NE is equal to water then it is considered as transparent nature.[15] |
| Stability | Determine the stability of the NE in different temperature conditions. | Stability chamber at different temperature condition and check the visual appearance, globule size, zeta sizer, UV-vis spectroscopy. | No or less change in the appearance indicates the stability of NE.[15] |
| **Thermodynamic stability:** Tested through stress tests like heating-cooling cycles, freeze-thaw cycles, and centrifugation to ensure the system does not undergo phase separation, creaming or cracking. | | | |
| **Heating and Cooling cycle:** NE was kept on a temperature ranging from 4°C to 45°C for six consecutive cycles. The stable formulation was selected for centrifugation test.[16] | | | |
| **Centrifugation test:** The selected stable formulation was centrifuged at 3500 rpm. Those formulations shows no phase separation was further selected for freeze thaw test.[16] | | | |
| **Freeze-Thaw cycle:** The selected formulation was kept on a temperature ranging between 21°C and 25°C for three consecutive cycles and it is carried out for almost three months.[16] | | | |

| Evaluation of Bioavailability and Therapeutic properties | | | | |
|---|---|---|---|---|
| **Name of the test** | **Determination** | **Method** | **Apparatus** | **Ranges** |
| Antioxidant activity test | Determines the antioxidant activity of NE | DPPH ABTS assay Total phenolic content analysis. | UV-VIS Spectrophotometer (absorbance measured at DPPH- 517 nm, ABTS- 743 nm, total phenolic content- 765 nm) | Reducing the DPPH and ABTS radicals by fading the color and loweringthe absorbance value means good antioxidant activity. Higher the phenolic content higher antioxidant activity.[14,17] |
| Antimicrobial activity analysis | Determine the antimicrobial activity using different microbes or pathogens and measures zone of inhibition (ZOI), minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) | Agar well diffusion assay, Microbroth dilution method, Agar dilution, time kill assay | - | At lowest concentration MIC means stop growing, MBC means dead or no colony grown and larger ZOI indicates highly effective NE.[3,7,17] |
| Physicochemical Integrity | To ascertain the significance of globule size on the integrity of the NE. | - | Dynamic Light Scattering(DLS) and Zeta potential | Droplet size less than 100 nm with high electrostatic stability.[14] |
| Morphological Stability | To evaluate globule size distribution and its impact on Ostwald ripening. | - | Cryo-TEM Imaging | Uniform globule distribution without oil phase separation or ostwald ripening.[15] |
| *In vitro* dissolution and permeability | To evaluate the dissolution of NE in the in vitro setup.<br><br>To evaluate the permeability of NE in the in vitro setup.[16] | 1) Dialysis Bag Method.<br><br>2) Caco-2 Cell Monolayers. | - | - |
| *Ex Vivo* absorption | To evaluate the permeation of NE and its rate through animal skin. | - | Franz Diffusion Cell System | Enhanced skin permeation or mucosal flux coefficients over |

| | | | | |
|---|---|---|---|---|
| | | | | time.[12] |
| *In vivo* Efficacy | To evaluate the efficacy of the NE within a living system. | Appropriate animal model. | Biomarker Expression (ELISA/ Western Blot) | Down regulation of inflammatory or oxidative stress markers in tissue.[14] |

**Application of Essential oil based Nanoemulsion**

Essential oils show enhanced physicochemical and functional properties when formulated as nanoemulsions, making them ideal and effective for topical applications. EOs based NE are used in pharmaceutical industry for wide range of biological and therapeutic activities.Byselectingappropriate EO and optimizing other formulation parameters, nanoemulsion can be developed for the management of moderate to chronic diseases. They may be utilized for the management of various dermatological conditions and skin-related disorders such as skin cancer, surgical wounds, dermatitis, diabetic foot ulcers, wound healing, burns, eczema and acne etc. Further, clove and lemon based EOs, has been shown to possesses antioxidant, analgesic, antifungal, antibacterial, anti-inflammatory and moderate to high antimicrobial activities.[4,6,7]

## CONCLUSION

EO based nanoemulsions are considered as one of the most promising delivery system.Their nano-size droplet improves stability, solubility, and bioavailability while promoting better permeation, especially when applied topically. EOs like clove and lemon enhances the potential of NE for its rich phytochemical compositions and biological activity. Such EOs altogether exhibit antimicrobial, antifungal, anti-inflammatory, analgesic and a broad spectrum of antibacterial activities.

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18. Pictures are Created in https://BioRender.com