Nat. Volatiles & Essent. Oils, 2021; 8(4): 8185-8201

NVEO
Natural Volatiles & Essential Oils

Nanoparticles Loaded with Essential Oils via Ultrasonication Technique: Overview, Challenges and Prospects

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Abstract

Essential oils have been used for bactericidal, virucidal, fungicidal, antiparasitic, insecticidal, and other medicinal properties such as analgesic, sedative, anti-inflammatory, spasmolytic, and locally anaesthetic remedies since the Middle Ages. Essential oils are complex concoctions of a wide range of volatile molecules, terpenoids, phenol-derived aromatic components, and aliphatic components are examples of compounds with a strong interest in the pharmaceutical, sanitary, cosmetic, agricultural, and food industries. The effectiveness of essential oils, on the other hand, is determined by their stability and bioactivity. Ultrasonication technique is one of the best methods to approach for conservation of essential oils. It provides numerous advantages, including improved water solubility, effective degradation protection, and prevention of volatile component evaporation. In this review, focuses on the most outstanding contributions of nanotechnology in essential oils formulated via Ultrasonication technique. We emphasise the chemical composition of essential oils, the principle of Ultrasonication technique, the physicochemical properties of nanoparticles loaded with essential oil, and their current applications. Essential oils can perform as well as or better than chemically synthesised drugs. The occurrence of oil nanoencapsulation has been observed as a cost-effective method and the ultrasonication technique is a simpler, less energy-consuming, more reproducible, and widely valid method for the encapsulation of essential oils when compared to other formulation techniques.

Keywords: Essential oils, Nanoencapsulation, Ultrasonication and Drug delivery System.

Introduction

With the popularity of alternative medicine, interest in essential oils has resurfaced in recent decades. Medical applications offered by individuals who sell medicinal oils range from skin treatments to cancer treatments, and are frequently based purely on historical records of essential oils being used for these purposes. Most countries now regulate claims about the effectiveness of medical therapies. Essential oils have been used in traditional Indian medicine, known as "Ayur Veda," for more than 3000 years.

Over 700 compounds are listed in Vedic literature as useful for healing, including cinnamon, ginger, and sandal wood. During the Bubonic Plague outbreak, Ayur Veda was successfully employed to replace inadequate antibiotics. Aromatic plants and oils were not only used for therapeutic purposes, but they were also thought to be a divine aspect of nature that contributed to Ayurvedic medicine's spiritual and philosophical approach.

Hippocrates, who is widely regarded as the father of medicine, mentions a variety of therapeutic and medicinal plants in his writings. Avicenna, an Arabic physician who lived in the 10th century, left us significant written materials outlining 800 different plants and their effects on the human body [1].

Essential Oils

Chemical Composition of Essential Oils

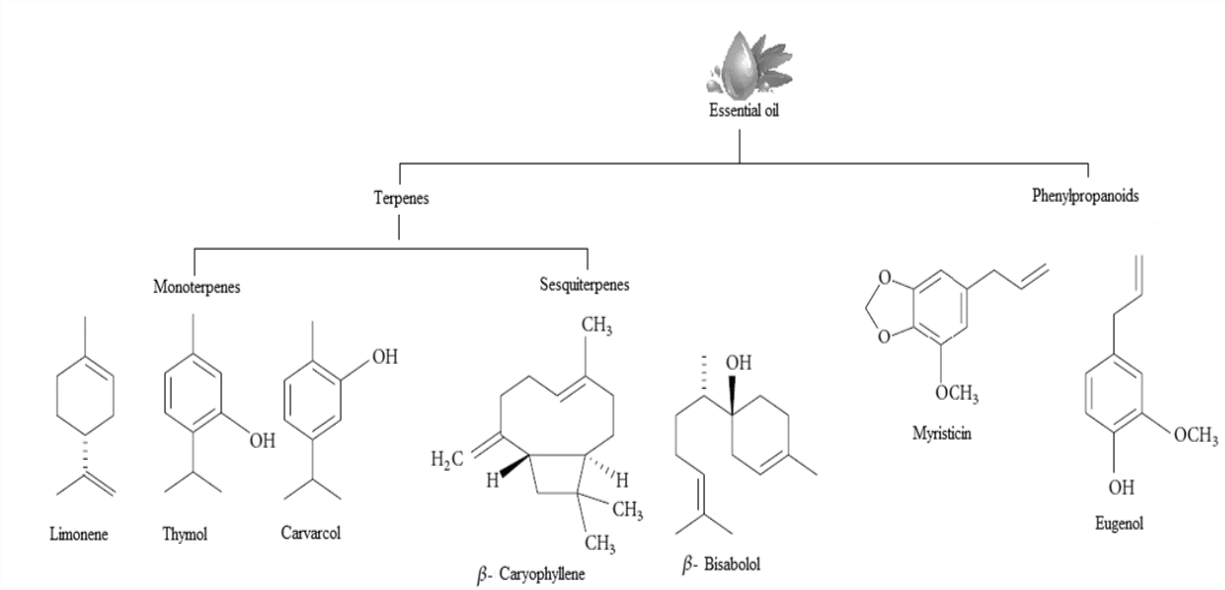
Essential oils (EOs) are lipid soluble and soluble in organic solvents with a density that is often lower than that of water. They are volatile, limpid, and rarely coloured liquids. EOs are produced in secretory cells, cavities, canals, epidermic cells, or glandular trichomes by all plant parts, including buds, flowers, leaves, stalks, twigs, seeds, fruits, roots, wood, or bark. Constituents are lipophilic, extremely volatile secondary plant compounds with molecular weights less than 300 that can be physically isolated from other plant components or membranous tissue [2].

EOs can now be extracted using a variety of techniques like use of liquid carbon dioxide or microwaves, as well as low- and high-pressure distillation using boiling water or hot steam, are all possibilities.

The word "essential oil" is reserved by the International Organization for Standardization (ISO) for a "product derived from vegetable raw material, either by distillation with water or steam, or by mechanical method, or by dry distillation" (ISO9235,1997), that is, exclusively by physical means. Furthermore, essential oils used in medicine must adhere to national or international pharmacopoeias. The chemical profile of essential oil products varies not only in terms of the amount and types of molecules present, but also in terms of their stereochemical structures, and can be quite varied depending on the extraction method used [3].

EOs are complex mixture of terpenic hydrocarbons, particularly monoterpenes and sesquiterpenes, as well as oxygenated derivatives such as aldehydes (citronellal, sinensal), ketones (menthone, p-vetivone), alcohols (geraniol, -bisabolol), phenols (thymol), and esters (-tepinyl acetate, cedryl acetate) [4]. EOs also contains non terpenic compounds known as phenylpropanoids and gives them their distinct flavour and odour. This group of compounds includes eugenol and cinnamaldehyde [5]. The chemical structure among several essential oil ingredients is shown in diagram (Fig.1).

Figure 1. Chemical Structures of few essential oil constituents



Challenges and Limitations to the Use of Essential Oils in Clinical Practice

Essential oils have recently been used as antioxidants and food preservatives [6]. Traditionally Eos been used for bactericidal, virucidal, fungicidal, antiparasitic, insecticidal, and other therapeutic qualities such as analgesic, sedative, anti-inflammatory, spasmolytic, and locally anaesthetic therapies [7,8,9].

Using essential oils or their components in therapeutic goods for human or animal use has been reported as a promising technique so far [10]. The promising way to use Eos external application, such as gargles and mouthwashes, or inhalation, is the most effective way to utilise Eos, they are rarely taken orally, even though they are generally considered as safe. When used orally, essential oils are usually diluted with milk, soy milk, or olive oil. Topical application is generally harmless, the oil is diluted in a formulation, but some oils (particularly citrus oils) are UV sensitive and may cause irritation or discoloration of skin when exposed to sunlight for up to four days after application. In case of inhaling strong oils through nasal route of administration, limit your time near an essential oil diffuser because the concentrated vapours might cause eye irritation. Some essential oils are not suggested for diffusing or direct inhalation.

Despite the fact that essential oils are quickly digested, there is sufficient data to show that their distribution throughout the body is relatively high. The majority of essential oil components are metabolised and either excreted in the form of polar molecules by the kidneys after limited phase I enzyme metabolism by conjugation with glucuronate or sulphate, or exhaled as CO2 by the lungs. For example, 35 percent of the original menthol content was eliminated renally as menthol glucuronide after oral administration of (-)-menthol [11,12].

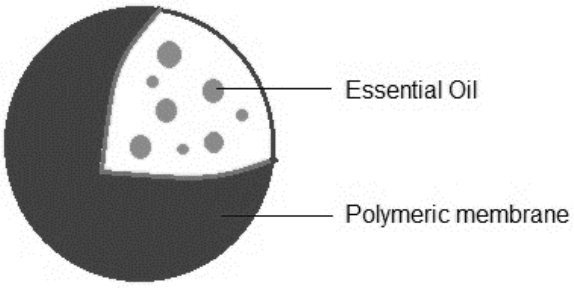
The fast metabolism and short half-life of active compounds in EOs have led to belief that there is a low chance of accumulating in body tissues [13]. EO compounds are small fat-soluble molecules that can pass through membranes, including the skin, before being collected by the microcirculation and emptied into the systemic circulation, where they reach all target organs [7,14]. EOs can irritate the skin, especially if they are not diluted. Excessive application of highly concentrated oils to a large surface area of the skin or on broken skin can cause significant systemic absorption and raise the risk of serious side effects like convulsions.

Aside from their high volatility, EOs decomposes quickly when exposed to heat, humidity, light, or oxygen. A recent manuscript looked at the factors that influence essential oil stability; understanding the chemical composition and properties of essential oils is critical for effective use [15]. Oxidation, isomerization, cyclization, and dehydrogenation reactions triggered either enzymatically or chemically, are responsible for the degradation of EO constituents [16]. Conditions during the processing and storage of plant material, distillation, and subsequent handling of the oil all have a big impact [17]. In addition to organoleptic and viscosity changes, some aged essential oils and oxidised terpenoids have skin-sensitizing properties [18], resulting in a hypersensitivity reaction similar to allergic contact dermatitis [19].

Techniques for Nanoencapsulation

Nanoencapsulation is the technology of capturing nanoparticles of solid, liquid, or gas, also known as the core or active, within a secondary material, known as the matrix or polymeric membrane, to form nanocapsules [20] (Fig.2).

Figure 2. Nanocpsule loaded with Essential Oil.



Encapsulation of bioactive compounds is a practical and effective way to control drug release, increase the physical stability of active ingredients, protect them from environmental interactions, reduce volatility, improve bioactivity, reduce toxicity, and improve patient compliance and convenience [21].

Nanocapsules range may falls in size from 1 to 1000 nm and comes in different shapes, depending on the materials and methods used to formulate them [22].

Nanoencapsulation is now accomplished using a variety of ways which are Chemical, physicochemical, and physicomechanical encapsulation procedures. These three of them are most often used techniques now a day [23]. The Chemical and physicochemical processes refer to approaches that involve chemical reactions in the development of nanocapsules. In contrast, no chemical reactions are involved in the synthesis of nanocapsules in physicomechanical procedures, and only shape fabrication is normally done. A few of the most often utilised approaches are briefly discussed in Table 1.

Table 1. Approaches for Nanoencapsulation.

Nanoencapsulation technique	**Methods Involved**
Sol–gel	(a) Solution of core and polymer (b) Formation of Sol phase (c) Gelation (d) Solidification
In situ polymerization	a) Preparation of core solution (b) Addition of droplets of monomer
Coacervation	(a) Formation of a three-immiscible chemical phases (b) Deposition of the coating (c) Solidification of the coating
Rapid expansion of supercritical solution	(a) Preparation of solution of core and shell materials in CO2 (b) Depressurization through a nozzle
Liposome entrapment	(a) Microfluidization

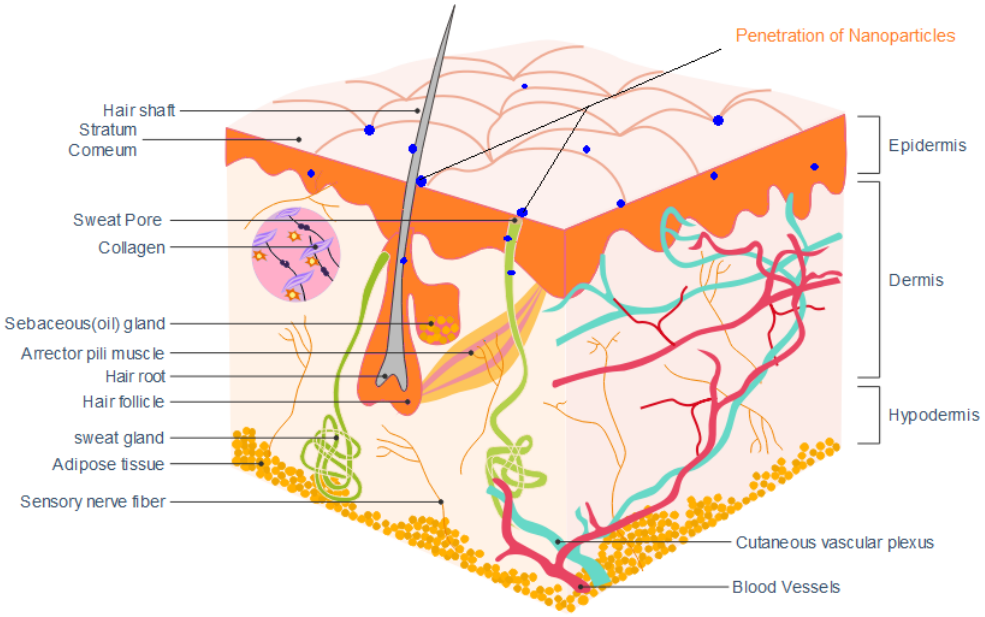
	(b) Ultrasonication
	(c) Reverse-phase evaporation
Spray-drying	(a) Preparation of a dispersion
	(b) Homogenization of the dispersion
	(c) Atomization of the dispersion
Solvent evaporation	(a) Preparation of solution of polymer and core
	(b) Solvent evaporation by heating
	(a) Preparation of core solution and wall solution
Electro coextrusion	(b) Simultaneous spraying of two solutions from two coaxial capillaries

Nano based drug delivery system

Nanosystems applied to the skin are used to facilitate local therapies even though the mechanisms of penetration through skin are still being debated. It is generally accepted that topical drug delivery with nanoparticles targets the nanoparticles to the deeper layers of skin and does not reach the viable epidermis. However, enhanced particle penetration occurs only when the cheratine barrier is compromised, as in aged or diseased skin. The use of nanoparticles allows for the sustained and slow release of active constituents; nanoparticles serve as a reservoir. Furthermore, nanoparticles can interact with skin at the cellular level as adjuvants to improve immune reactivity in topical vaccine applications [24].

Hair follicles and furrows were previously thought to be insignificant as potential drug delivery routes because they covered less than 1% of the human skin surface area, but their complex vascularisation and deep invagination with a thinning stratumcorneum have caused a rethinking of this viewpoint. It has been shown that hair follicles, in particular, are an efficient reservoir for nanoparticle-based drug delivery, and that massage can increase nanoparticle penetration [25]. The surface of the skin, furrows, and hair follicles are all potential sites for skin-targeting nanoparticles, as shown in (Fig 3). Oral intake and inhalation are the two alternative routes of administration for Eos [26]. The mucosal linings of the nasal, lung, oral (sublingual and buccal) cavity, stomach, and gut are all encountered by nanodelivery systems along these routes. Nanocarriers can improve the stability of EOs against enzymatic degradation, achieve desired therapeutic levels in target tissues for the required duration with fewer doses, and may ensure an optimal pharmacokinetic profile to meet specific needs.

Figure 3. Skin nanoparticle drug delivery



Ultrasonication Process to Encapsulate EO's

Principle

The ultrasonic method is one of the rapidly emerging techniques developed to reduce processing, improve quality, and ensure the safety of food products [27]. Ultrasound technology, a key area of research and development in the food industry, is based on mechanical waves at a frequency above the human hearing threshold (>16 kHz) and is classified into two frequency ranges: low and high energy [28]. Low-energy (low power, low intensity) Ultrasound has frequencies greater than 100 kHz at intensities less than 1 Wcm2, whereas high-energy lasers have frequencies greater than 100 kHz at intensities greater than 1 Wcm2 (high power, high-intensity) Ultrasound employs intensities greater than 1 Wcm2 at frequencies ranging from 20 to 500 kHz [29]. The representative frequency range commonly used in ultrasonic technology is between 20 kHz and 500 MHz [30]. As an analytical technique, high-frequency ultrasound is used to determine the physicochemical properties of food, such as acidity, firmness, sugar content and ripeness, etc. Low-frequency ultrasound, on the other hand, is used to change the physical and chemical properties of food [31] by inducing pressure, shear, and temperature differences in the medium through which they propagate [32], and it is capable of producing cavitations to inactivate microorganisms in foods [33]. The typical frequency limit for ultrasound applications is between 20 kHz and 500 MHz [30].

Mechanism of action

When ultrasound is applied to liquid systems, it causes acoustic cavitation, which is the phenomenon of bubble generation, growth, and eventual collapse (Fig 4). As the ultrasound waves travel, the bubbles oscillate and collapse, resulting in thermal, mechanical, and chemical effects.

Mechanical effects include collapse pressure, turbulence, and shear stresses [30], whereas chemical effects include free radical formation [34]. Extremely high temperatures (5,000 K) and pressures are generated by the effects in the cavitation zone (1,000 atm) [31].

Depending on the frequency of the ultrasound, locally generated alternating positive and negative pressures cause material expansion or compression, resulting in cell rupture.

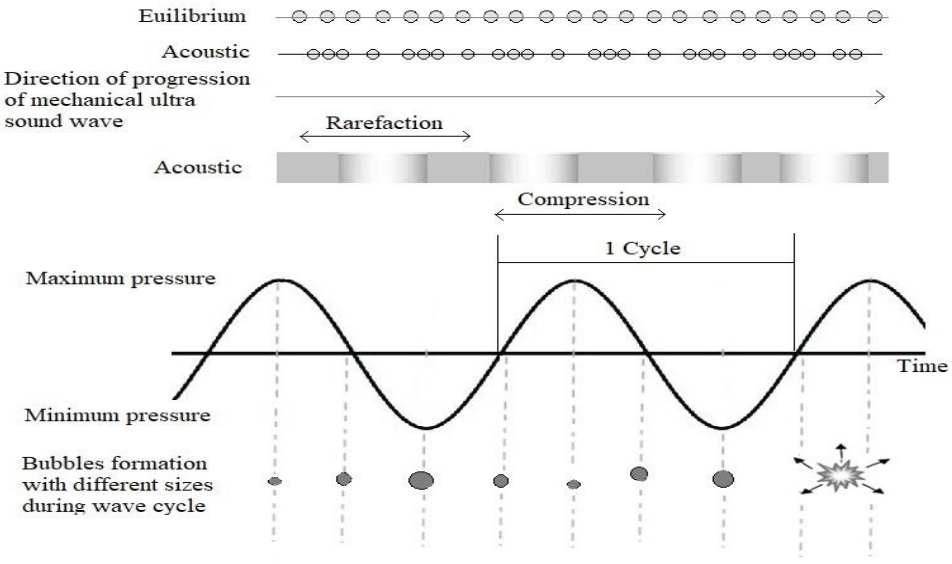
Ultrasound causes hydrolysis of water inside oscillating bubbles, resulting in the formation of H+ and OH free radicals that can be captured in some chemical reactions, such as free radical scavenging by amino acids of enzymes involved in structure stability, substrate binding, or catalytic functions [28].

This sonication disruption effect is significantly resisted by homogeneous liquids. Bubbles produced during sonication treatment are classified into two types based on their structure:

a) Stable cavitations bubbles are non-linear bubble clouds that form large bubble clouds with an equilibrium size during pressure cycles.
b) Internal (transient) cavitation bubbles are non-stable bubbles that rapidly collapse and disintegrate into smaller bubbles.

These small bubbles dissolve quickly, but during bubble stretching, the mass-transfer boundary layer is thinner and the interfacial area is larger than during bubble collapse, implying that more air enters the bubble during the stretching phase than leaks out during the collapse phase [35].

Figure 4. Ultrasonic cavitation



Types of ultrasonication apparatus

The ultrasonicator is a tool that helps to intensify homogenization procedures. which facilitates the effective and simultaneous splitting of particles spread throughout the liquid. In general, an ultrasonicator is used for a variety of purposes. such as dispersing nanoparticles in base fluids to minimise agglomeration [36], to reduce nanoparticle size in a fluid or during nanoparticle synthesis and surface functionalization [37]. There are two types of sonicators utilised in various applications: a) bath type sonication and b) probe type sonication (Fig 5) [38]. the bath type ultrasonic devices having the minimal intensity [39] (10–40 W/L) and effect on the particles are negligible. The probe sonicator, on the other hand (>=20000 W/L), is a more intense sector with a more focused influence and uniform concentration in the fluid [40].

Since ultrasonic probes can generate energy more efficiently, cover a larger area, and focus on nature, they are better suited for thermal-based applications. Obviously, larger diameter probes have more thermal properties. At the point of action, different types of probes have varying intensities. The larger probe point generates a greater number of disturbances than the pinpoint probe. Particle size reduction and emulsification probe are suitable for rapid and localised applications, whereas bath is suitable for applications such as cleaning apparatus and degassing. In conclusion, the probe type is the most commonly used type in nanofluids.

Figure 5. Probe type Ultrasonication

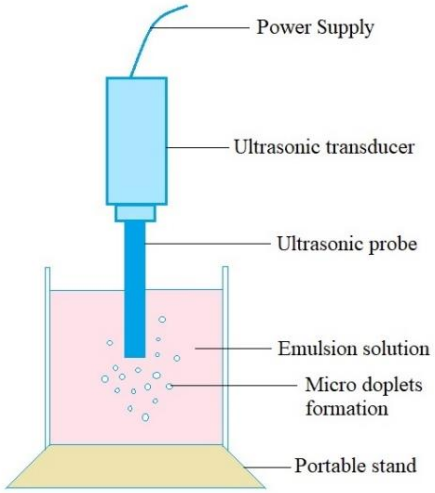


Table 2. Ultrasonication method for preparation of nanoparticles loaded with essential oils.

S.No	Source of Essential Oil	Surfactants	Size of the particles	Biological Properties	References
1	Linum usitatissimum	Tween 80,	67.3 nm to 82.6 nm	Antioxidant Property and Bactericidal Activity	(Keykhasalar et al., 2020)
2	Myristica fragrans	Montanov 82	217.4 nm maximum limit <500nm	Phyto-Repellant	(Narawi et al., 2020)
3	Apium graveolens	Tween 80	23.4 ± 1.80 nm.	Anticancer and Antibacterial Activity	(Nirmala et al., 2020)
4	Anise (Pimpinella anisum), artemisia (Artemisia vulgaris), fennel (Foeniculum vulgare), lavander (Lavandula angustifolia), peppermint (Mentha x piperita), rosemary (Rosmarinus officinalis) and sage (Salvia officinalis)	Span 80, Span 20, Tween 80, and Tween 20,	116 ±2 nm (Artemisia) to 188 ±2 nm (Sage).	Insecticidal activity	(Campolo et al., 2020)
5	Origanum vulgare and Helianthus	sodium octenyl succinic anhydride modified starch	(180±0.94nm), 226 nm and 265 nm	Oregano Essential oil exhibits antioxidant, antimicrobial, anti-carcinogenic, and anti-inflammatory properties	(Espinosa et al., 2021)
6	Cinnamomum zeylanicum	Polysorbate 80 (Tween 80)	242–362 nm	anti- microbial, mechanical, barrier and microstructural properties	(Reza et al., 2020)
7	Thymus vulgaris	Soy lecithin	137.9nm to 180.3 nm	anti-microbial effect	(Xiuxiu et al., 2020)
8	Cymbopogon citratus	Tween 80 (1%v/v)	between 35 and 4 nm	anti-microbial activity	(Laura Salvia et al., 2014)
9	Eucalyptus globulus	Tween 80	9.4nm	larvicidal activity	(Sugumar et al., 2014)
10	(Citrus reticulata × Citrus sinensis	tween 80 and span 80	66.2 nm and 42.9 nm	antibacterial ability	(Doan et al., 2020)

11	Linum usitatissimum and Fish	Polyoxyethylene glycol sorbiton monooleate (Tween-80)	62.3 nm and 112.9 nm	Anti-oxidant and antibacterial activity	(Hashim et al., 2019)
12	Eugenia caryophyllus	Kolliphor P188(poly (ethylene oxide) - poly (pro-pylene oxide))	10 nm	alopecia areata	(Stephani et al., 2020)
13	Syzygium aromaticum and Origanum vulgare	Tween 80 Poly ethylene glycol (PEG)	180−250 nm	Anti-microbial films	(Otoni et al., 2014)
15	Citrus limon	Span 85 (sorbitane trioleate) and brij 97 (polyoxyethylene oleyl ether)	<100 nm	Anti-microbial activity	(Lu, W. C. et al., 2018)
16	Borago officinalis L	purity gum ultra (PUG)	186-364 nm	Anti-oxidant activity	(Rehman et al., 2020)
17	Cocos nucifera Linn, GarciniamangostanaLinn (mangostin extract)	Span 20 and Tween 20	18–62 nm	Anti-bacterial and Anti-oxidant activities	(Sungpud et al., 2020)
18	Plukenetia volubilis Linneo	poloxamer 407 (pluronic f127)	<100 nm	Antioxidant activity	(Elgegren et al., 2019)

Applications

Due to the beneficial properties of essential oils have gained a foothold in a variety of fields. EO's biological effects have currently been extensively documented [41,42]. Table 2 summarizes some research studies on the application of EO-loaded nanoparticle (NP) prepared via the ultrasonication process.

Agriculture Field

Environmental risks to humans, flora, and fauna, as well as the development of resistance in pathogenic microorganism species, have increased significantly in recent decades as a result of the indiscriminate use of synthetic agrochemicals such as pesticides, herbicides, and insecticides. Today, the use of natural compounds, particularly EO, in agriculture has risen to prominence [43,44,45]. Aspergillus flavus and Aspergillus parasiticus are common food spoilage organisms that produce secondary metabolites or mycotoxins that are carcinogenic and cause fatal diseases in both animals and humans. Luque-Alcaraz et al. recently investigated the inhibitory effect of Schinus molle L. EO loaded chitosan NP on the filamentous fungi Aspergillus parasiticus involved in the spoilage of fruits, vegetables, or other carbon-rich substrates [46]. Chitosan appears to be a biologically compatible polymer with a significant impact on the control of phytopathogenic fungi, Gram positive and Gram-negative bacteria [47,48,49].

Food Field

The most common method of postharvest disease control is the use of synthetic food preservatives; however, due to consumer awareness of the use of synthetic additives, formulations based on low toxicity and more environmentally friendly compounds are more desirable. As a result, natural extracts such as EO or their main components that are Generally Recognized as Safe (GRAS) are effective alternatives to synthetic products. Several studies have shown that EO can be used as an antimicrobial and antioxidant in food packaging [50]. In 2017, Sotelo-Boyas and colleagues used a nanoprecipitation technique to create Citrus aurantifolia Christm. EO loaded-NP and tested their antibacterial activity against four food-borne bacteria: Staphylococcus aureus, Listeria monocytogenes, Shigella dysenteriae, and Escherichia coli are all examples of pathogens. Shigella dysenteriae exhibited the greatest inhibition, with an inhibition halo diameter of 3.5 cm for 40 mL of minimum inhibitory volume [51].

Several studies have been published that used in situ assays with coating formulations containing EO-loaded nanosystems on fresh fruits to investigate their shelf life and evaluate any damage caused by microorganisms. In this context, Pia-Barrera et al. proposed a promising food packaging system based on Thymus vulagris L. EO loaded-Eudragit L 100-55 nanoparticles for grape preservation against foodborne bacteria [52].

Medicinal Field

The ability to form biofilms plays an important role in the pathogenesis of many microbial diseases [53,54] and infections associated with medical devices [55]. Simultaneously, indiscriminate antibiotic use has resulted in the emergence of multi-drug-resistant bacterial pathogens [56]. As a result, growing concern about bacterial infection management is driving the urgent replacement of existing antibiotics. Essential oils appear to be effective in dealing with such issues [57]. Carvacrol, the main component of

several EO, has piqued the interest of researchers due to its broad antimicrobial spectrum and ability to inhibit the growth of preformed biofilms and interfere with biofilm formation. Using the solvent displacement technique, it was encapsulated in poly(lactide-co-glycolide) nanocapsules [58].

Cosmetic Field

Nowadays, EO are widely used in cosmetic products due to their ability to improve the properties and preservation of the product, as well as to provide a marketing image to the final product. Several research studies have been conducted in order to incorporate EO into cosmetics and personal care products. Jummes et al. recently discovered Cymbopogon Martinii Roxb. EO-loaded-NP as a cosmetic antioxidant alternative to synthetic antioxidants [59]. In comparison to free EO emulsion, the developed particles demonstrated high antioxidant activity against DPPH free radicals and improved antibacterial activity against Staphylococcus aureus and Escherichia coli [59]. For example, cosmetic lotion formulations containing encapsulated thymol suppressed viable bacteria growth completely over a three-month test period, whereas free thymol suppressed viable bacteria growth for only 2–4 weeks [60].

Textiles

In recent decades, the use of essential oils (EO) has spread to the textile domain, and a substantial amount of research has been conducted on the benefits of aromatherapic textiles [61]. Lavandula dentata L. oil was efficiently entrapped in NP prepared from the diblock copolymer (PEO-b-PLA) for use as an antibacterial agent in textile components used in the footwear industry [62]. Several parameters must be considered when functionalizing textiles, including the affinity between the active agent and the textile during the application process.

Conclusion

Currently, researchers are focusing most of their efforts on developing new approaches to preserve the essential oils stability, bioactivity, and bioavailability, as there is growing concern that essential oils can perform as well as or better than chemically synthesised drugs. The occurrence of oil nanoencapsulation has been observed as a cost-effective method of overcoming such constraints. According to the literature discussed above, the ultrasonication technique is a simpler, less energy-consuming, more reproducible, and widely valid method for the encapsulation of essential oils when compared to other preparation methods. For example, it provides the best nanoparticles in terms of size and encapsulation efficiency. The management of operating conditions and the selection of raw materials are critical steps in obtaining formulations with suitable properties for in vitro and in vivo applications. Scale-up the use of nanoparticles for the delivery of essential oils is one of the most recent approaches in pharmaceutical technology, so Ultrasonication technique in industries is an important factor to be consider.

Abbreviations

EO: Essential Oil; EOs: Essential Oils; ISO: International Organization for Standardization; NP: Nanoparticle; kHz: kilohertz; MHz: Megahertz; K: Kelvin; atm: atmosphere; OH: Hydroxide, H: Hydrogen; nm: Nano meter; PEG-b-PLA: Poly (ethylene glycol)-b-poly (lactic acid); PEG: Poly ethylene glycol; PUG: purity gum ultra; mL: Millilitre; V/V: volume/volume; W/L: Watt per litre; GRAS: Generally Recognized as Safe; DPPH: 2,2-diphenyl-1-picrylhydrazyl.

ACKNOWLEDGEMENT

We are very thankful to Chalapathi Institute of Pharmaceutical Sciences (AUTONOMOUS), Guntur, Andhra Pradesh for providing facility to carry this work.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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