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Essential oils in pharmaceutical technology:

A review on commonly used formulations

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1. Summary

Essential oils are precious herbal medicinal products derived from plants using increasingly efficient extraction techniques. They contain multiple components that make them therapeutically rich and challenging to formulate. The formulations commonly used today by the public for different routes of administration are often simple homemade forms such as various inhalation devices, inert tablets, pieces of sugar, honey, self-filled capsules or various fats for the vaginal and rectal routes of administration. Essential oils are also used in cooking. Liposomal formulations like Disper and Solubol are often used in pharmacies for oral administration. There are few comprehensive studies on the pharmacokinetics of essential oil constituents and even fewer conclusions on their bioavailability according to their route of administration. The cutaneous bioavailability of essential oils can nevertheless be estimated at 10% (Tisserand 2014). Of course, each of the constituents has a different bioavailability and is influenced positively or negatively by their companions. Oral bioavailability is more difficult to estimate. It is greatly influenced by food, as learned from the food industry, which investigated the activity loss of antimicrobial activity in the presence of food.

Advanced drug delivery systems are very successful with essential oils. Microemulsions with a diameter of 10-50nm using essential oils as solubilizers can be obtained and allow an improvement of bioavailability (Nirmala 2013). Nanoemulsions with a droplet diameter of 70nm also enabled an improvement in bioavailability (Zhao 2010). An encapsulation efficiency of 45% was obtained with cyclodextrins, improving the stability and antimicrobial activity of the essential oil of *Achillea millefolium* (Rakmai 2017). While essential oil loaded liposomes had a mean size of 470 nm and 65 nm for Large Multilamellar Vesicles (MLV) and Small Unilamellar Vesicles (SUV) respectively, the encapsulation of essential oils in liposomes is apparently easy if one considers that the encapsulation efficiency is by far above 50% and even 98% in one example and that one can obtain a stability of at least 6 months at 4-5°C (Sherry 2013).

Essential oils, Christmas market, Bern 2017

2. Introduction

Essential oils are complex blends of a variety of volatile molecules such as terpenoids, phenol-derived aromatic components, and aliphatic components having a strong interest in pharmaceutical, sanitary, cosmetic, agricultural, and food industries. Essential oils are widely used for their bactericidal, virucidal, fungicidal, antiparasitic, insecticidal effects and other medicinal properties such as analgesia, sedation and anti-inflammatory spasmolytic activities as well as for locally anesthetic remedies (Bilia 2014).

Essential oils, also known as essences, volatile oils, etheric oils, or aetheroleum, are natural products. According to the International Standard Organization on Essential Oils (ISO 9235: 2013) and the European Pharmacopoeia (EDQM 2019) an essential oil is defined as the product obtained from plant raw material by hydro distillation, steam distillation or dry distillation or by a suitable mechanical process (for Citrus fruits). The definition of an essential oil excludes other aromatic/volatile products obtained by different extraction techniques such as solvent extraction, supercritical fluid extraction, and microwave-assisted extraction (Zuzarte 2015).

The yield of distillation for obtaining essential oils is for instance of 0.02% (carrot seeds), 0.5% (roman chamomile or 20% for cloves, and is in general around 1%, for instance for officinal lavender. It depends on the content of essential oils in the plants, but also the solubility of essential oils in water, their density and the quality of the distillation itself. Today we obtain essential oils of very good quality at very advantageous prices considering the work load.

Salvia Sclarea L., Bettina Fehlmann, La Tour-de-Peilz

New extraction techniques for essential oils from plants are used nowadays: headspace trapping, static headspace, vacuum headspace, dynamic headspace, solid phase

micro-extraction, supercritical fluid extraction, phytosol extraction, protoplast technique, simultaneous distillation extraction, microwave distillation, controlled instantaneous decomposition, thermomicrodistillation, microdistillation, molecular spinning band distillation, membrane extraction (Buckle 2015).

In the perfume industry, most modern essential oil production is accomplished by extraction using volatile solvents such as petroleum ether and hexane. The chief advantages of extraction over distillation is that uniform temperature (usually 50° C) can be maintained during the process. As a result, extracted oils have a more natural odor that is unmatched by distilled oils, which may have undergone chemical alteration by the high temperature. This feature is of considerable importance to the perfume industry; however, the established distillation method is of lower cost than the extraction process (Buckle 2015).

In aromatic plants, the composition of essential oils usually varies considerably because of both intrinsic (sexual, seasonal, ontogenetic, and genetic variations) and extrinsic (ecological and environmental aspects). Genetic variations may result in the expression of different metabolic pathways and, consequently, quantitative and qualitative variations in essential oil composition may occur. When significant differences are found, an intraspecific category (chemotype) is defined. Essential oil quality strongly depends on all these factors that may interfere and limit plant yield. Analytical guidelines published by several institutions such as the European Pharmacopoeia, International Standard Organization (ISO), and World Health Organization (WHO) are available and must be followed to ensure the good quality of the commercialized essential oils and of the plants from which they are obtained. In general, the industries choose the chemotypes that have most commercial interest, to obtain high-quality end products as well as efficient biological activities. Quality assessments of essential oils include sensory evaluations, very common in perfumery houses; physical and chemical tests, required in standards, pharmacopoeias, and chromatospectral techniques for oil analysis. “Notwithstanding the achievements in analytical techniques, the total separation and identification of all compounds of the volatile mixture remains unattainable because of the large number of compounds, structural similarities, isomeric forms, and concentration range of the compounds present. Moreover, compounds with similar mass spectra and identical retention indices make essential oil characterization a very difficult task” (Zuzarte 2015).

Steam distillation, l'Essencier, Icogne

Steam distillation, distillerie de Bassins sarl

3. Aromatherapy

René-Maurice Gattefossé (1881–1950) discovered aromatherapy through an accident. In 1910, while working in his laboratory, he was burnt in an explosion. He ran outside and rolled on the grass to extinguish the flames. A few days later the wounds became infected with gas gangrene but "one rinse of essential oil of lavender *(Lavandula angustifolia)"* stopped the infection.

Lavandula angustifolia, Bettina Fehlmann, La Tour-de-Peilz

Impressed, Gattefossé dedicated his life to researching essential oils. Many of his patients were soldiers wounded in the trenches of World War I. He used essential oils such as thyme, chamomile, clove, and lemon. Until World War II, those essential oils were used to disinfect wounds and to sterilize surgical instruments. “Gattefossé is thought to be one of the first people to use the word *aromatherapy.* He discovered that essential oils take between 30 minutes and 12 hours to be absorbed completely by the body after being applied topically. His work *Aromatherapie: The Essential Oils—Vegetable Hormones* was published in France in 1937” (Buckle 2015).

Matricaria chamomilla L., Bettina Fehlmann, La Tour-de-Peilz

In 2008, the Gateffossé Foundation was established by Sophie Gattefossé–Moyrand to pay tribute to her grandfather. In 2010, the 44th Journée Galéniques (annual meeting held at Gattefossé’s home) was dedicated to the future of aromatherapy in healthcare.
“Throughout World War II, French physicians used essential oils on infected wounds and as a treatment for gangrene. Perhaps the course of aromatic medicine. would have been different if Alexander Fleming had not discovered a piece of moldy bread that led to the manufacture of penicillin. With the emergence of manufactured antibiotics, full of promise, profit, and easy availability, essential oils fell by the wayside” (Buckle 2015).

Salvia Officinalis, Distillerie de Bassins sarl

The European Pharmacopeia contains a specific monography for the quality of essential oils as well as numerous monographies of essential oils.
The Committee on Herbal Medicinal Products of the European Medicines Agency published in 2014 a reflection paper (EMEA) about essential oils raising many issues from a regulatory standpoint. Current guidance does not address fully the aspects of essential oils and further guidance is needed for manufacturers of essential oils and applicants on the documentation to be presented to the competent authorities. The Interested Parties have provided examples and comments covering the range of different manufacturing processes which are specific for essential oils. Important points raised were the feasibility of a GMP compliant manufacturing process of the active substance. The quality of water used for the distillation of oil from fresh plant material performed in the fields was another point of discussion. The blending of sub batches and the compliance of such sub-batches with the Ph. Eur. monograph was important. Furthermore, the committee on herbal medicinal products published several essential oil monographs called community herbal monographs e.g. for mint and thyme about the therapeutical use of those.

Thymus Vulgaris L., Distillerie de Bassins sarl

Aromatherapy products are generally classified as a cosmetic, a drug or both by the FDA (FDA 2018).

To illustrate the current use of essential oils in Switzerland, we describe hereunder two examples of pure essential oils registered by Swissmedic as herbal medicinal products.

Lasea is an essential oil of lavender formulated in vegetable oil of rapeseed in capsules to be taken orally in case of anxiety and agitation, once a day, corresponding to 80mg of essential oil.

The Japanese mint oil JHP Rödler is used as an internal treatment for digestive disorders and for colds. In addition, it is used as an external treatment in the form of friction in case of muscular pains, to relieve headache and as inhalation.

Mentha piperita, Bettina Fehlmann La Tour-de-Peilz

The list of registered herbal medicinal products in Switzerland can be found on the internet site of the Swiss Medical Society of Herbal Medicinal Products (SMGP/SSPM Phytopharmaka in der SL (Spezialitätenliste) https://www.smgp.ch/smgp/homeindex/arzneimittel.html)

3.1 Clinical trials

The therapeutic effectiveness of essential oils is reflected in the frequency of their use, yet clinical trials are complicated by the very nature of essential oils and their multi-complexity. There are few examples of clinical trials using essential oils in the literature. One them is exposed here.

This study was designed to assess the olfactory impact of the essential oils of lavender (*Lavandula angustifolia*) and rosemary (*Rosmarinus officinalis*) on cognitive performance and mood in healthy volunteers. One hundred and forty-four participants were randomly assigned to one of three independent groups, and subsequently performed the Cognitive Drug Research computerized cognitive assessment battery in a cubicle containing either one of the two odors or no odor (control). The findings indicate that the olfactory properties of these essential oils can produce objective effects on cognitive performance, as well as subjective effects on mood (Moss 2003).

In the last 15 years, the methods of evidence based medicine dominated the medical research. It allies different study methods: meta-analysis, randomized controlled study and observation studies. Although usually very strict in the review of clinical trials, the Cochrane collaboration in addition to randomized controlled studies also sees the utility of observation studies to obtain clinical evidence. “Nevertheless, one difficulty among others in the investigation of clinical studies with the use of plants is the fact that the

preparations used are often not adequately analyzed and characterized, and preparations are often pooled" (Melzer 2017).

3.2. Dosage of essential oil

The database Aromadoc (Fehlmann 2018) presents a full scheme of the dosages of essential oils considering their route of administration, in adults, children and women in pregnancy:

- Orally for adults, the usual dose is 20-30 drops of a 10% formulation of essential oils in Disper, Solubol or Fludol in a large glass of water 3 times a day corresponding to 80-150mg of pure essential oil 3 times a day.
- For the rectal route, 200-250mg of essential oil 2-3 times a day and for the vaginal route, 300mg 2-3 times a day are described.
- The concentration of the essential oil in dermal applications is of 1-3% in dermocosmetic use, 5-10% for an activity on muscles, tendons and articulations, 20% for a systemic activity, 30-50% for high local antiseptic or antifungal activity, or pure for essential oils above any suspicion.
- The importance of the risk incurred for an exhaustive list of essential oils containing ketones or lactones according to the oral, dermal, rectal or vaginal route of administration is presented.

The Swiss Medical Society for Phytotherapy published the following recommendations for the use of a list of essential oils in small children in the Age < 30 months on doctor's prescription (SMGP/SSPM https://www.smgp.ch/smgp/homeindex/arzneimittelf/dokumente/Empfehlungsliste_Terpene.pdf):

Suppositories for infants < 30 months: Mixture of 3-5 essential oils.
Recommended dose of essential oils per suppository: 0.050 g, 1-3 times daily depending on age. These recommendations apply also for pregnant women.
Nevertheless, each essential oil should be evaluated individually.
For older children, other essential oils may also be used, and the dose may not exceed 0.1 g per suppository.

Ketones, along with lactones, are the most delicate components to handle because of their toxicity. It is a neurological (neurotoxicity) and obstetric (abortifacient) toxicity. It is important to respect the doses of administration and to consider the accumulation of doses (do not administer in the long term) (Tauxe 2012, personal communication).

Essential oils are perfect for personalized patient care. Indeed, there is more and more talk of a lack of comprehensive care for the person, including his or her psychological state. The preparation of essential oil blends seems ideal for this purpose.

The question arises whether a formulation containing ten different essential oils for a maximum total dose of 80-150mg given 3 times a day contains enough of each of the

constituents to obtain a plasma level in the therapeutic range. Some of those constituents will hit the same receptors in the body and the activity will cumulate, but for others, the threshold of concentration on one receptor class might not be reached.

Essential oils correspond to complex natural mixtures which can contain around 20-60 components at concentrations which can vary significantly. Normally the mixtures are characterized by two or three major components present at high concentration compared to other components present in smaller amounts. So called type chromatograms are published in the European Pharmacopeia.
By chance, these natural constituents mainly result from five to six pathways of biosynthesis, which reduces the possibilities for structural variations and allows their regrouping according to their toxicity level and metabolism. Consequently, most of the main constituents are identified and can be assessed from a toxicological point of view. The main challenge results from the quantitative variations that can be observed for each of the constituents according to the process of extraction and the biological history of the plant. Significant variations can be observed between different batches of essential oil of Lavender extracted by the same company using the same procedure, but the plants are from different harvests. It is therefore essential that an essential oil is fully chemically characterized to be able to define the variation acceptable for each of its main constituents. (Masson 2010)

3.3. Classical routes of administration of essential oils

The administration routes most commonly used for administering essential oils include dermal, oral, inhaled, nasal, buccal, vaginal and rectal routes.

“Essential oil compounds are small, fat soluble molecules, able to permeate the membranes including the skin before being captured by the microcirculation and drained into the systemic circulation, which reaches all targets organs. In general, the respiratory tract offers the most rapid way of entry followed by the dermal pathway” (Bilia 2014).

Essential oil components seem to be quickly absorbed after oral, dermal and inhalational administration, though there is a general lack of good quality pharmacokinetic data in humans. Peak serum concentrations of some constituents administered by different routes depend on the route of administration. Typically, after inhalation, the peak is reached after 20 minutes and 100-360 minutes after oral administration. The maximal amount of essential oil constituents absorbed from dermal application can be rounded to 10% (Tisserand 2014).

There is little information on the pharmacokinetics of essential oil by oral administration and the other routes of administration. In any case, information is gathered only on the compound which is taken as a reference, but all the other compounds eventually could have a different metabolism and distribution in other organs and not necessarily in the target organ according to the route of administration. Therefore, an inhaled essential oil, might present another metabolic profile than the same oil taken orally, and the organ targeting will be different. Moreover, the psychological effect certainly plays a role. If you apply drops of mint on the forehead for treating headache, some of it will be bioavailable, not through a direct route into the brain, but as it is close to the head, it will act on the person's psychic by passing through the nose, and in parallel, the active ingredient will be absorbed by the skin and the general distribution in the body.

There are still many unknowns about the pharmacokinetics of essential oil components. Depending on their absorption route, they also bind and metabolize differently (sulphates or glucuronides) and their activity is modified.

3.3.1. Dermal administration

Essential oils are lipid soluble and many of the components can be absorbed through the skin rapidly. Carvone, a ketone in essential oils, was found in the bloodstream of a human subject within 10 minutes of a massage. The dermal penetration and absorption of several essential oils such as lemon (Valgimigli 2012), eucalyptus (Karpanene 2010), tea tree (Reichling 2006), juniper (Gavini 2025) and rose (Schmitt 2010) using a specific main constituent as marker have been published. In aromatherapy massage, essential oils are usually applied to the skin diluted in a vegetable oil vehicle. Recipients may benefit in three ways: from absorbing essential oil constituents through the skin, from absorbing constituents via inhalation, and from the massage itself (Tisserand 2014). Friction, caused by massage, encourages dilation of blood vessels in the dermis and can increase the absorption of essential oil components.

The cosmetic and pharmaceutical formulations using essential oils are usually tailored by dispersing them on semi solid media. To stabilize the formation of emulsions a wide range of emulsifiers is used. Considering the high hydrophobic nature of essential oils, various fat-like excipients have been applied on development of creams, ointments, foams, cosmetic butters and lotions. Most of preparations are made for topical usage, and among them O/W types emulsions are preferred due to their better spreadability on the skin, as well as to avoid the awkward residual oily sensation after product application. Considering the natural antimicrobial profile of several essential oils their use can lead to a reduced demand of synthetic preservative excipients like parabens which possess known allergenic potential.

Caution should be taken when applying essential oils to damaged skin, because damaged skin can be more absorbent and more likely to have adverse reaction. Damaged skin includes skin affected by systemic disease, dermatological problems, injury, dehydration caused by a cold, dry environment, stress, or the daily use of strong detergents or exaggerated use of pure essential oils. As skin ages it becomes thinner, its barrier function becomes diminished and therefore essential oils are absorbed faster.

Most essential oil constituents can cross the stratum corneum to the epidermis. They can be stored in the epidermis for up to 72 hours, or reach the dermis and from there enter the blood supply. Several recently published studies show how components within essential oils such as citronellol and geraniol (Gilpin 2010), linalool (Lapczynski 2008), and terpinen-4-ol (Cross 2006) are absorbed through the skin. The least lipophilic components (i.e., most water soluble) of tea tree, such as terpinen-4-ol and a-terpineol, most easily penetrated the skin. Bergapten—a component of bergamot *(Citrus bergamia)*—was found in the blood 4 hours after it had been applied to the skin diluted in jojoba oil. (Buckle 2015).

The kinetics of absorption depends on the weight of the molecule and certain physicochemical properties, such as polarity and optical activity. Differences in optical

rotation may be the way to differentiate between oils from two species, and optical rotation can affect absorption and polarity and optical activity can affect how essential oil component are absorbed into the body (Tisserand 2014).

Essential oils and their volatile constituents can penetrate through the skin as well as enhance penetration of different drug from topical formulation into the lower skin layers using different mechanisms of action based on (1) disintegration of the highly ordered intercellular lipid structure between corneocytes in stratum corneum, (2) interaction with intercellular domain of protein, which induces their conformational modification, (3) increase the partitioning of a drug (Herman 2015).

Major components of lavender (linalyl acetate and linalol), tea tree (γ-terpinene and terpinen-4-ol), grapefruit (limonene) and cypress oils (α-pinene and 3-carene) from aroma bath showed that their dominant percutaneous absorption were observed after 10–20 min bathing of mice. Limonene from grapefruit oil showed the highest degree of percutaneous absorption,and was detected not only in blood but also in brain and lung after 20 min bathing of mice. Also, main constituents of lavender oil (linalool and linalyl acetale) from massage oil penetrated the skin of male volunteers, and their maximum concentrations were detected in the blood after 20 min. However, 90 min after the end of massage, most of the lavender oil constituents was eliminated from the bloodstream.
In male rats after dermal treatments the disposition of citral from essential oils was studied. It showed that 5 min after the treatment, no unmetabolized citral was detected in their blood. It is worth mentioning that more citral was eliminated in the feces than in the urine.

The fact that after application to the skin, essential oils and their components are rapidly metabolized, not accumulated in the organism and rapidly excreted strongly suggest that they can be successfully used as safe penetration enhancers (Herman 2015).

The skin barrier function is accomplished entirely by the outermost few microns of the skin, the stratum corneum. The lipid matrix and the stratum corneum architecture play an instrumental role in the barrier function of the membrane. The skin represents a large surface area (1-2 m^2) for absorption. The molecules crossing the stratum corneum will need to have the necessary physicochemical properties, Ideally, a drug must possess both lipoidal and aqueous solubilities: if it is too hydrophilic, the molecules will be unable to transfer into the stratum corneum: if it is too lipophilic, the drug will tend to remain in the stratum corneum layers. The ideal limits suggested for passive transdermal according to (Naik 2000) are: aqueous solubility >1g/l; lipophilicity $10<K_{o/w}<1000$; molecular weight <500Da; melting point <200^oC; pH of saturated aqueous solution pH 5-9; dose deliverable <10 mg/day ($K_{o/w}$ being the oil-water partition coefficient).

A convenient measure of the relative solubility of a substance in lipid and aqueous media is its partition coefficient (P), usually expressed in its logarithmic form, $\log_{10}$ P. For the dermal absorption of essential oil constituents, an optimum log P value of 2–4 (for the n-octanol/water system) has been proposed.

Constituent	Log_{10} P
Benzyl alcohol	1.1
Vanillin	1.2
Guaiacol	1.3
Coumarin	1.4
Benzaldehyde	1.5
(*E*)-Cinnamaldehyde	1.9
Benzyl acetate	2.0
Bergapten	2.0
Methyl salicylate	2.3
Eugenol	2.4
Isoeugenol	2.6
α-Terpineol	2.8
1,8-Cineole	2.8
Methyleugenol	2.9
Terpinen-4-ol	3.0
Citral	3.0
Methyl isoeugenol	3.1
Estragole	3.1
Thymol	3.2
(*E*)-anethole	3.3
(+)- and (−)-Linalool	3.4
Carvacrol	3.4
(+)- and (−)-Citronellol	3.6
Linalyl acetate	4.1
γ-Terpinene	4.4
α- and β-Pinene	4.4
(+)-Limonene	4.5
α-Santalol	5.0
α-Terpinene	5.5
Nerolidol	5.7
Farnesol	5.8
δ-Cadinene	6.5

$Log_{10}P$ (octanol/water) values for some essential oil constituents (Tisserand 2014)

In a study comparing a wide range of compounds, including some essential oil constituents, a highly significant linear relationship between percutaneous absorption across excised human skin in vitro and octanol/water log P values, and an inverse relationship with molecular mass, was found (Tisserand 2014).

Some components of essential oils cross easily the skin, and penetrate in deeper zones of the skin, but others do not penetrate and remain in the stratum corneum. Further, some components will act as penetration enhancers.

Essential oils have shown the potential to reversibly overcome the stratum corneum barrier to enhance the skin permeation of drugs. Terpenes are the main constituents of essential oils and consist of isoprene units. They have been proposed as promising nontoxic, nonirritating penetration enhancers for both hydrophilic and lipophilic drugs (Jiang 2017). Terpenes mainly act on the intercellular lipid structure between corneocytes to increase the fluidity of stratum corneum lipids. In addition, combination of terpenes can also increase the permeation enhancement effect.

Turpentine and essential oils were investigated for the capacity and mechanism to promote skin penetration of ibuprofen. Essential oils can promote the skin permeation of ibuprofen mainly by disturbing rather than dissolving the stratum corneum lipids. To-date, essential oils have been shown to be successful in delivering a range of different drugs across the skin, including vitamins, estradiol, diclofenac sodium, indomethacin and others (Jiang 2017).

The enhancement permeation capacities of the whole essential oils were proved to be significantly higher than its main terpene components. For example, Niaouli oil and its main terpene components (1,8-cineole, a-pinene, a-terpineol and D-limonene) were compared as penetration enhancers to promote permeation of estradiol through skin (Jiang 2017).

3.3.2. Oral administration

There is a long history of essential oils being given to patients orally by doctors and nurses before the advent of modern pharmaceuticals. The oral route is perfectly safe and nontoxic provided the dosages are carefully measured.
Essential oils that are high in phenols should be diluted and encapsulated to avoid mucous irritation when administered orally.

The fear of using essential oils orally is based on three things: a) a lack of knowledge, b) fear of poisoning and c) fear of litigation because the oral use of essential oils is perceived in many countries to be practicing medicine without a license.

For oral administration, gelatin capsules are commonly used. They are filled with 20% essential oil(s) diluted in vegetable oil. Numerous tutorials for homemade capsules can surprisingly be found on internet.

Disper is a lecithin-based emulsifier that contains 70% ethanol beside of phospholipids, glycolipids and amino acids it holds the essential oils in a stable dispersion. 10 drops (or parts) of Disper are mixed with each drop (or part) of essential oil used, then water is added to create a milky emulsion. Up to 10% essential oil can be diluted in Disper. It is a more fluid solution than Solubol and Fludol.

Solubol and Fludol are alcohol-free emulsifiers that contain water, vegetal glycerin, fatty acids, sunflower triglycerides, coprah extract, soya lecithin, beeswax, propolis extract, rosemary extract, Vitamin E and Vitamin C. Up to 20% of essential oils can be diluted in Solubol or Fludol, which allows a good dispersion in water. Golgemma produces Solubol which has a registered trademark in France since 2006.

Essential oils can also be blended with honey, taken as such or added to a glass of warm water. Enteric-coated gelatin capsules do not release the essential oil until they are in the small intestine (an environment of pH 6.8 or higher). This can be useful for irritable bowel syndrome (Holmes 2016).

Essential oils are excreted through the kidney, lungs and skin. Following oral administration, essential oil components are mainly excreted in the urine. However, components may also be excreted in the exhaled breath or in the feces. There is limited information about excretion of essential oils in humans.

The transit time of food through the stomach and gastrointestinal tract varies greatly depending on individuals, their age and health status, and the type of food they eat. A liquid containing essential oils ingested on an empty stomach can pass in a few minutes into the intestine, but when a food bowl is present, gastric emptying takes about 2 hours. The transit time at the small intestine level takes about 4 hours and 50 hours at the colon level (wikipedia). The stability and the bioavailability of the constituents of the essential oils might vary greatly depending on transit time and food effect.

The usual dosage of essential oils of 80-150mg 3x/day for oral administration (Aromadoc) correspond to a theoretical concentration of 0.32-0.6g/l in the stomach considering a volume of 250ml. The solubility of essential oils in water being usually of 1-2g/l, we can assume that the essential oils are soluble in the stomach. Further, the body temperature certainly improves the solubility of essential oils.

The first series of Food and Drug Administration guidelines for scale up and post approval changes (SUPAC) introduced the concept of Biopharmaceutical Classification System (BCS) based on solubility and permeability of the drugs. Drugs are grouped into four classes as given below. Four categories are defined by two quantitative terms; first, a dimensionless dose to solubility ratio using 250 ml as intestinal volume, and the

second apparent permeability coefficient in cm/sec across Caco-2 cells. The range of these two values for BCS

Class I: High solubility ≤0.5 + High permeability >$1x10^{-5}$
Class II: Low solubility >1 + High permeability >$1x10^{-5}$
Class III: High solubility ≤0.5 + Low permeability <$2x10^{-6}$
Class IV: Low solubility >1 + Low permeability. <$2x10^{-6}$

These predictions for extent of absorption based on drug biopharmaceutical properties are strongly related to *in vivo kinetics* of drug dissolution and intestinal permeation. (Palamakula 2004).

In our theoretical considerations above, we can assume that essential oils present a dose to solubility ratio <0.5 and, therefore situated in class I or class III of the BSC depending on the permeability parameter. We do not have here data on the permeability of essential oils across Caco-2 cells to evaluate the bioavailability using BCS, especially since they do not consist of a single compound.

Essential oils are complex mixtures of components with different physicochemical characteristics influencing one another and their permeability behavior towards the intestinal barrier. Essential oil components have even been used as permeability enhancing excipients in advanced drug delivery systems. The in vivo performance of Coenzyme Q-limonene based self-nanoemulsified drug delivery systems provided a 4.7-fold increase in the bioavailability of Coenzyme Q as compared to control (Palamakula 2004).

Synergistic effects can be produced if the constituents of essential oils affect different permeability pathways or interact with one another to improve the solubility and thereby enhance the bioavailability of one or several components of an essential oil. Bioavailability of essential oils can be improved by adapted drug delivery systems like nanoparticulate systems.

To determine the systemic availability and the pharmacokinetics of thymol after oral application to humans, a clinical trial was carried out in 12 healthy volunteers. Each subject received a single dose of a Bronchipret® TP tablet in an empty stomach. The combined amount of both thymol sulfate and glucuronide excreted in 24-hour urine was 16.2% ± 4.5% of intake. Thymol was rapidly absorbed. Thymol sulfate could be detected in plasma 20 minutes after application. The plasma concentration versus time profile was biphasic, subdivided into a distribution phase and a slow terminal elimination phase beginning at about 10 hours after administration and lasting up to an average of 38 hours (Kohlert 2002).

In various studies, the quantities of essential oils that have been taken orally by adults over a 24 hours period range from 0.05–1.3 ml. The typical oral dosage range (0.22–

0.66 ml) is approximately ten times greater than the amount typically applied by massage (0.03–0.06 ml) (Tisserand 2014). It was assumed that 100% of any oil administered orally is absorbed and it is mentioned that there is little information concerning the safety of oral dosing over a period of several days or weeks

3.3.3. Inhalation route

Due to their large surface area, rich blood supply, and the thin membrane separating air and blood, the lungs are very efficient organs for the absorption of gases and volatile substances from the air. The lungs have a huge surface area that is intimately connected to the blood system via the alveoli. Inhaling essential oils is the fastest method of getting essential oils into the body. When we inhale essential oils, components can travel to the lungs, the brain, or both (Holmes 2016). The lipid solubility enables small molecules within essential oils to cross the blood-brain barrier which prevents many substances in the blood accessing the brain. Odors can affect our brains by influencing the production of neurotransmittors. Receptors in the brain respond to chemical structures, odor molecules, within the essential oil. Indirect inhalation can be achieved by heating water in a bowl or with various devices like burners, fans, humidifiers, diffusers or nebulizers and aromastones.

3.3.4. Nasal administration

All findings confirm that most essential oils are rapidly absorbed after dermal, oral, or pulmonary administration and cross the blood-brain barrier and interact with receptors in the central nervous system, and then affect relevant biological functions such as relaxation, sleep, digestion etc. “The nasal cavity is an easily accessible route which is generally well tolerated. The abundance of blood vessels in the nasal mucosa contributes to drug absorption, which is almost equal to intravenous injections in some instances” (Ghori 2015).

The delivery from the nose to the central nervous system may occur via the olfactory neuroepithelium and may involve paracellular, transcellular and/or neuronal transport with this olfactory pathway presenting the potential to bypass blood brain barrier. The nasal route can also be a useful alternative to the oral route for drug absorption in situations where a use of the gastrointestinal route is unfeasible. The extent of drug absorption may depend on many physicochemical properties including acid-base dissociation constant and partition coefficient, molecular weight, particle size and solubility of the drug. In general, for a drug to be absorbed it must be in solution and this can be problematic for drugs with low solubility. Nasal drug delivery has the unique capability to bypass the hepatic first pass metabolism and direct delivery of drugs to the

brain (Ghori 2015).Nasal drops typically contain 1% essential oil, 9% Fludol or Solubol, and 90% of an isotonic hydrolat (Aromadoc).

The mucous membranes of the nasal cavity and pharynx also contribute to gas exchange. The significance of the lungs as ports of entry to the body is reflected in the presence of important local detoxifying enzymes. Essential oils may be used in environmental or steam inhalation, or applied to the chest.

“The essential oil constituents can be sensory irritants. The respiratory tract is intimately connected with the ears and eyes by a mucous membrane, and thus exogenous irritants may affect tissues at one or more of these different anatomical sites. The irritant and sensitizing actions of many, often aged, essential oils have been ascribed to oxidation products of various constituents, especially unsaturated compounds” (Tisserand 2014).

The evaluation of literature data on essential oil stability revealed that oxidative changes and deterioration reactions, which may lead to both sensory as well as pharmacologically relevant alterations, have scarcely been systematically addressed. “Especially temperature, light, and oxygen availability are recognized to have a crucial impact on essential oil integrity. The importance of extrinsic storage factors on the physicochemical stability of essential oils revealed that this issue still awaits profound scientific evaluation” (Turek 2013).

3.3.5. Buccal administration

Mouthwashes and gargles containing essential oils or their components are excellent for dental issues, mouth or throat infections, gingivitis or to help reduce radiation-induced oral mucositis, candidiasis in AIDS or a simple sore throat. For the latter, three drops of an essential oil are added to15 ml of warm water for a gargle.

3.3.6. Vaginal administration

Essential oils can be effective in vaginal suppositories, douches or in creams against local candidiasis, using for instance tampons with three to five drops of essential oil and 5 ml of carrier oil against vaginal infections. Vaginal routes have a distinct advantage in the treatment of gynecological or urinary conditions because the essential oils are absorbed directly into the surrounding tissue. One can find on the internet a multitude of recipes for making homemade ovules or homemade systems for local application of essential oils at the vaginal level. It is mainly to treat local fungal infections.

3.3.7. Rectal administration

Essential oils can be successfully used in rectal pessaries or rectal suppositories and ointments. Applied rectally, essential oils can be used to treat local affections like hemorrhoids or systemic absorption to treat for instance bronchitis. Although this route of administration is not well known in the Anglo-Saxon countries, it is widely used in Europe. Administering essential oils via the rectum allows the components to be quickly and well absorbed into the blood stream via the highly vascularized tissues in the rectum and avoiding the first pass effect. This is an effective route of administration for systemic treatments like for instance for respiratory and gastrointestinal diseases as well as local treatments like bacterial, fungal and inflammatory affections.

It is interesting to observe on the internet a lot of advice on how to prepare suppositories containing essential oils at home. There are improvised suppository molds, like ice cube trays, to be placed in the freezer before and after the incorporation of a few drops of essential oil in coconut oil into the middle zone. This fat melts at body temperature. You can read: “do it yourself essential oil rectal implants help support a healthy colonic mucosa. Essential suppositories for hemorrhoids, constipation, and candida overgrowth provide healing for these and other colon-related ailments”.Despite the fact that the population is generally well informed by Internet, the risk of an inappropriate dosage of essential oils is in our view very real in these situations of homemade medications.

There are several advantages to administration by the rectal route, because the absorption site is near the administration site. The high concentration of essential oil in the rectum may initiate a permeation enhancing effect of individual constituents on the other constituents. We can expect that essential oil constituents administered rectally have a faster onset, higher bioavailability, shorter peak, and shorter duration than the oral route. Also, the rectal route bypasses usually the first pass effect. This means the individual molecules contained in the essential oil are expected to reach the circulatory system with significantly less alteration and in greater concentrations than by the oral route. Typical factors that allow for high absorption from the rectal route of administration are high partition coefficient, small molecular size, low charge, and low capability of hydrogen bond formation which are the physicochemical properties of many constituents of essential oils. The topic of rectal bioavailability of essential oils would certainly merit further investigation in our view.

3.4. Advanced drug delivery systems

Essential oils and essential oil isolated pure components are lipophilic and have limited solubility in water, mostly below 2 g/l at around 20°C. (Chen 2014).
The solubility in water is an essential parameter for distillation and extraction techniques of essential oils, but also of course, for formulation techniques.

3.4.1. Nanosystems

An improved use of essential oil in herbal medicinal products will mainly be driven by improved technological applications to decrease volatility, improve the stability, water solubility and efficacy of essential oil formulations. Nanoencapsulation is one option available.
Nanoparticles can solve the major inconvenience of essential oil use increasing the chemical stability in the presence of air, light, moisture and, high temperatures, factors which can lead to the rapid evaporation and to the degradation of the active components. In addition, nanocarriers ensure the easier and safer handling of the liquid substances by changing them in solid powders, determining retention of volatile ingredients and taste masking, setting up controlled release and/or consecutive delivery of multiple active ingredients, reducing toxic side effects, improving water solubility of hydrophobic ingredients, and enhancing bioavailability and efficacy. Nanoencapsulation of essential oils in liposomes, solid lipid nanoparticles, nano- and microemulsions, and polymeric nanoparticles represent an excellent strategy for overcoming essential oils limitations, lowering their dose.

Nanoencapsulation can potentially prevent the degradation of essential oils. Besides the high volatility, essential oils can easily decompose, owing to direct exposure to heat, humidity, light, or oxygen. Degradation of essential oils constituents is due to oxidation, isomerization, cyclization, or dehydrogenation reactions, triggered either enzymatically or chemically, strongly influenced by the conditions during processing and storage of the plant material, upon distillation, and during subsequent handling of the oil itself (Bilia 2014).

Preparations based on essential oils have some important limitations. It is not recommended to expose the skin directly to essential oils because of potential irritations. Nanoencapsulation technologies has been quoted as an alternative for overcoming these problems (Pedro 2013).

Nanoparticles can accumulate on the surface of the skin and within the subcutaneous tissues and penetrate deeper into the skin through the hair follicle or the sudorific path.

3.4.2. Microemulsions

Due to the drawbacks such as low solubility and low oral-bioavailability essential oil based microemulsion systems as a drug delivery vehicle have been designed. A microemulsion typically consists of oil, surfactant and water in required and optimized proportions. Essential oils can be used as solvents in microemulsion systems to carry themselves or to solubilize a non-soluble active ingredient. Microemulsion systems include detergent, active ingredient, essential oil and water and are thermodynamically stable. Different essential oils can be used to solubilize active ingredients in microemulsion systems such as cinnamon oil, mustard oil, tea tree oil and clove oil.

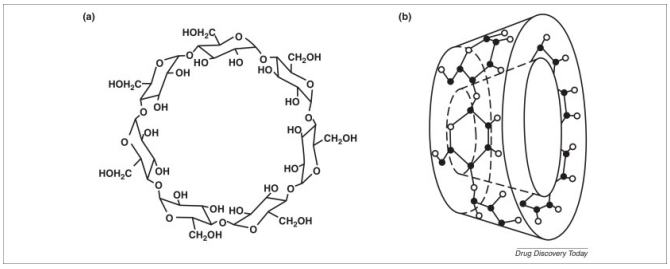
When the microemulsion meets a mucous membrane or skin, it allows to obtain a large surface of contact and a great absorption. Advantages of using a microemulsion are spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, improved drug solubilization of hydrophobic drugs and bioavailability. According to (Nirmala 2013), droplets of 9-48nm were formed in a cinnamon oil based microemulsion for ramipril with high solubilization potential; thus, improving bioavailability of the drug.

3.4.3. Nanoemulsions

A self-nanoemulsifying drug delivery system was developed for oral delivery of zedoary turmeric oil, an essential oil extracted from the dry rhizome of curcuma. The AUC curve with or without a nanoemulsified formulation containing ethyl oleate, tween 80 and transcutol P loaded with 30% of essential oil was used. It consisted of droplets with a mean size of 68.3±1.6nm. In rats, both AUC and C_{max} of germacrone, a representative bioactive marker, increased by 1.7-fold and 2.5-fold respectively compared with the unformulated essential oil. Absolute bioavailability was not measured (Zhao 2010)

3.4.4. Cyclodextrins

Cyclodextrins, have been extensively exploited by the food, pharmaceutical and cosmetic industry by their ability to entrap guest moieties. The poor solubility, the volatility and sensitivity to environmental factors of essential oils pose challenge for the formulation scientist. Inclusion complexes of essential oils into cyclodextrin has allowed to circumvent these challenges (Wadhwa 2017). Cyclodextrins may form inclusion complexes with essential oils to improve their characteristics, such as transformation of liquid compounds into crystalline form, masking unpleasant smell and tastes of some compounds; improving the stability; and stabilizing volatile compounds by reducing or eliminating any losses through evaporation. Complexation has also been used to avoid the destruction of certain flavors. The guest molecule is released in the warm moisture of the mouth (Cabral Marques 2000).

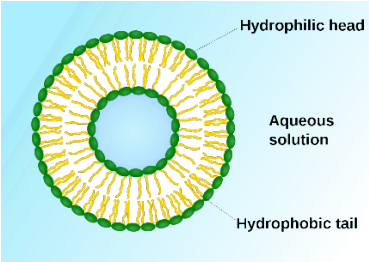


Cyclodextrins in pharmaceutical formulations, Jambhekar et al. (2016) Drug Discovery Today 21, 356-362

Essential oil from yarrow (*Achillea millefolium*) has a broad spectrum of pharmacological activities. However, active chemical components of yarrow oil are sensitive to environmental factors such as, light, oxygen and temperature. Yarrow oil was encapsulated in hydroxypropyl-β-cyclodextrin (HPβCD) through freeze-drying with encapsulation efficiency of 45%. Although encapsulation decreased the radical scavenging capacity, it could protect the active components against the effect of sunlight by 27–30%. The encapsulation also improved the antibacterial activity by four to eight times over the free yarrow oil revealing that the encapsulation in HPβCD can also decrease the minimum concentration of antimicrobial compounds needed for inhibition of microbial growth thanks to its solubilizing and stabilizing effect (Rakmai 2017).

3.4.5. Liposomes

Most essential oils are unstable. They are sensitive to oxygen, light and temperature. Therefore, encapsulation is applied to enhance their solubility and bioavailability, to protect them, as well as to control their release, hence, improving their efficacy (Sherry 2013).



Liposomes (26 December 2018) https://en.wikipedia.org/wiki/Liposome

Liposomes are spherical vesicles formed of an aqueous core and amphiphilic lipid bilayer They are usually classified according to their lamellarity and size such as multilamellar vesicles (MLV), which are large vesicles having size greater than 0.5 mm, small unilamellar vesicles (SUV), which are of sizes between 20 and 100 nm, and large unilamellar vesicles (LUV) that have sizes greater than 100 nm. Liposomes are biodegradable, biocompatible, nontoxic and nonimmunogenic. They can offer several advantages as carriers of the encapsulated molecules by enhancing their pharmacokinetics and biodistribution. Their structure can incorporate hydrophobic, hydrophilic and amphiphilic molecules (Sherry 2013).

Several authors have compared the size of empty liposomes to essential oil-loaded liposomes prepared at identical experimental conditions. In one example, important differences in the average size between empty and Santolina insularis essential oil loaded liposomes for both MLVs and SUVs were measured. Empty liposomes had a mean size of around 2200nm and 120nm for MLV and SUV, respectively, while essential oil loaded liposomes had a mean size of 470 nm and 65 nm for MLV and SUV, respectively. From these results, one may conclude that essential oils can decrease the sizes of liposomes. This effect was explained by the capability of essential oils to cause higher cohesion packing among the apolar chains in the membrane vesicles. On the other hand, it was demonstrated that monoterpenes can decrease the sizes of liposomes by forcing soybean phosphatidylcholine vesicles to increase their surface curvature. This suggested that the monoterpenes studied were located at the polar head group region of the membranes, which was enforced by the ability of the monoterpenes to increase differentially the polarity of the membrane environment (Sherry 2013).

The encapsulation efficiency (% of free essential oil found in the supernatant versus total essential oil in the sample) differs from one essential oil to another for liposomes

prepared by the same method. Typically, SUV dispersions give lower encapsulation efficiency than MLV, as seen for MLVs and SUVs encapsulating *Zanthoxylum tingoassuiba* essential oil had encapsulation efficiencies of 80% and 70% respectively. Similarly, *Artemisia arborescens* L. essential oil SUVs' encapsulation efficiency was 60%, which was less than that of MLVs, where MLVs' encapsulation efficiency was 70%. Another example, showed much higher encapsulation efficiency (98%) for *Anethum graveolens* essential oil (Sherry 2013). This difference in the encapsulation efficiency depends on the physico-chemical properties of each essential oil and/or on production technique, phospholipid/lipid composition and concentration, ratio between essential oil and phospholipids and cholesterol (Sherry 2013).

The encapsulation of essential oils in liposomes is apparently quite easy if one considers that the encapsulation efficiency is by far above 50% and even 98% in one example and that one can obtain a stability of at least 6 months at 4-5^{o}C (Sherry 2013). Liposomes are dynamic systems, allowing the multiple compounds of essential oils to migrate between the polar and apolar portions of the lipids of the bilayers and into the supernatant and back. When parenteral liposomes are administered, the free and encapsulated fractions must be reproducible and stable, but this does not concern essential oils which are not suitable for injection. For a non-parenteral administration where liposomes play an excipient role, this balance may have some flexibility.

When using phospholipids for oral administration of essential oils such as Disper and Solubol presented above, we are not only dealing with liposomes but complex mixtures of mixed micelles, emulsified droplets and unilamellar and multilamellar liposomes. The constituents of essential oils lodged in the oily phase or on surfaces, in interfaces or free dissolved in the external phase. When such dynamic systems are administered orally, some stability of these structures can be expected with respect to different digestive tract obstacles such as pH variations, food and bile salts. Ideally, the presentation of small particles on the surface of the gastrointestinal membrane should be preferred to achieve passage through the systemic circulation. Indeed, these commercial dispersing systems like Disper and Solubol described above are already very well adapted.

One can find tutorials on the internet to produce essential oil liposomes at home using an ultrasonic bath (Eytonearth 2018). The liposomes will not remain intact when taken orally,but might protect the essential oil components to be precipitated with food and allow bile salts to be integrated and produce adequate lipidic droplets for membrane permeation. The situation is very complex and not reproducible depending on whether one has eaten or not and according to the composition of the essential oil because each component can modify the partition in the gastrointestinal wall according to its solubility.

To measure the gastrointestinal passage of essential oils, representative molecules are used as analytical markers, the variability of the essential oil composition is certainly a challenge.

With liposomes, the potential contact area of essential oil with a surface is larger. They can migrate out of the bilayers and meet a surface to be disinfected, or the skin or the membrane of the gastrointestinal tract.

But liposomes do not pass through the skin, because they bind to the stratum corneum, in the same way as essential oil probably do, unless a high local concentration allows a percutaneous enhancer effect.

If you put essential oil on a piece of sugar or a tablet, it will not allow solubilization and a better passage, but maybe a positive effect due to the smell it gives off. In liposomes. it probably smells less due to the encapsulated essential oil.

3.4.6. Microencapsulation

Aromatic plants and their essential oils have been used since ancient times in food, agriculture, medicine, cosmetic applications, as condiments and spices, in therapeutic uses, as antimicrobials, as flavoring agents, and in storage as insecticidal agents (Krimer 2016). There are numerous publications describing the encapsulation of essential oil (nanoprecipitation, coacervation, spray drying, rapid expansion of supercritical solutions, encapsulation in liposomes, and encapsulation in solid lipid nanoparticles) showing a very good entrapment efficiency, especially considering liposomes. The difficulty in those technologies is indeed the loss of essential oil which could happen when mixed with the organic solvents involved.

Methods to extract essential oils from plants have greatly improved using supercritical CO_2 or microwave methods following the interest of many different industrial sectors, like pharmaceutical, medical, textile and food. (Asbahani, 2015) increasing the interest in microencapsulation techniques.

Biological effects of essential oils can be the result of a synergism of all molecules or can reflect only those of the main molecules present at the highest levels. Generally, the major components are found to reflect the physical and biological features of the essential oils; however, it is possible that the activity of the main components is modulated by other minor molecules. Yet, it is important to mention that both positive and negative synergism can occur between essential oils.

Considering the limitations of some processes and the physicochemical characteristics of essential oils, coacervation is an attractive technique to encapsulate this type of active agents. The most commonly used shell materials in coacervation are polysaccharides and sugars (gums, starches, celluloses, and cyclodextrins); proteins (gelatin, casein, and soy proteins); lipids (waxes, paraffin, and oils); and synthetic polymers (acrylic polymers and polyvinylpyrrolidone). To a lesser extent, inorganic materials such as clays, silicates, and polyphosphates can also be used.

Controlled released formulations allow smaller quantities of essential oils to be used and are highly effective over a longer period. The encapsulation process is a suitable method for entrapping essential oils of a very different chemical composition. This method reduces loss and has been applied to improve the sustained release effect, stabilization, and easy handling of essential oils. Materials, such as chitosan, gelatin, alginate, and poly(l-lactide), have biodegradability and environment-protecting properties. (Krimer 2016).

Microencapsulation has numerous industrial applications (Martins 2014). The selection of the technique and shell material for the microencapsulation of essential oils depends on the final application of the product, considering physical and chemical stability, concentration, required particle size, release mechanism and manufacturing costs. The encapsulated agent can be released by several mechanisms, for example, mechanical action, heat, diffusion, pH, biodegradation and dissolution. The best encapsulation results, which show that the coacervation technique reduces the loss of essential oils to a minimum, obtained for thymus essential oil in polylactic acid, a biodegradable polymer was 80% for the apolar compounds and 54% for the apolar ones. (Martins 2014).

The type of polymer and detergents used influence the encapsulation efficiency, and the technology allows evaporation and degradation of essential oils to be kept to a minimum. The dissolution curve of the microparticles is determined by the analysis of the major compounds showing a constant release of 5 days suggesting a complete release within 10 days. The shape of the dissolution curve strongly depends on the presence of polar and apolar compounds in the essential oil.

Polylactide is biodegradable and could in principle be administered orally. Since today we fear nanostructures, although biodegradable, we could imagine using microspheres rather than nanoparticles. For cosmetics, nanoparticles can easily be applied to the skin. They will not pass through the deep layers of the skin but rather stay at the stratum corneum and release the essential oil from there.

The encapsulation of essential oils in biodegradable polymers is to be considered case by case, In the current work, (Liakos 2016) have used the nanoprecipitation method to obtain PLA/Lemongrass essential oil nanocapsules without the use of additional polymers or surfactants. Lemongrass essential oils originate from steam distillation of lemongrass plant, and it is known for its antimicrobial properties even when encapsulated into polymers. Lemon grass essential oil consists of many molecules, such as hydrocarbons, aldehydes, alcohols, ketones and others. Thus, since it contains molecules with long chains with both hydrophobic tails and hydrophilic head groups, it is believed that it can act also as a surfactant for the preparation of PLA nanocapsules (Liakos 2016).

In view of the numerous publications found, it appears that essential oils can be formulated easily with the many different nano and microtechnologies available in industry.

4. Single essential oils constituents

Some essential oil constituents are isolated and used as pure chemical entities. Essential oils are liquid, lipophilic and volatile, but among their constituents there are compounds which are not volatile, and which can be solid at room temperature and solubilized by the other constituents of essential oils. Typical examples are thymol, linalool, carvacrol and menthol. Thymol is a phenol contained in thyme oil and in the essential oils (volatile) of many other plants. It is presented in the form of colorless crystals with a characteristic aromatic odor. It is soluble in alcohols, in fats and is not soluble in water. It is used among other applications as antibacterial and antifungal agent. Linalool refers to two enantiomers of a naturally occurring terpene alcohol in many flowers and spice plants. These have multiple commercial applications, the majority of which are based on its pleasant scent (floral, with a touch of spiciness. Linalool is used as a scent in 60–80% of perfumed hygiene products and cleaning agents including soaps, detergents, shampoos, and lotions. It is also used as a chemical intermediate.

Natural compounds often exhibit anti-inflammatory, antioxidant, antibacterial, antiviral, anticancer and/or tissue regenerative activity. Some natural products contain several bioactive molecules that synergistically provide therapeutic efficacy. For instance, bergamot essential oil consists of more than 345 compounds. Its fractions, have been found to exhibit anticancer efficacy. However, the poor water solubility, low stability and limited bioavailability have prevented the use of bergamot oil in cancer therapy. To overcome such drawbacks, Bergamot oil was formulated in liposomes that improved the water solubility of the phytocomponents and increased their anticancer activity in vitro against human SH-SY5Y neuroblastoma cells. (Celia 2013).

The goal of such studies is questionable because it seems quite out of reach to be able to develop intravenously administered liposomes with improved pharmacokinetics for tumor targeting. Further, the synergetic activity of whole essential oil will be lost in such formulations.

5. Essential oils in food

Solubility of essential oils is an important aspect in food technology too. It is well known that essential oils or their individual components perform well in antimicrobial assays conducted using microbial growth media, also called “in vitro” tests, but their effectiveness is much reduced in complex food matrices with compounds binding to them. The levels of essential oils used in in vitro tests, are usually within the solubility limit, but the level needed to achieve inhibitory and bactericidal activities in foods is highly dependent on composition. Typically, food matrices with hydrophobic food components, like proteins and lipids, can cause significant reductions in antimicrobial activities. Despite numerous studies on antimicrobial activities and speculation about food matrix interference, quantification of the solubility of essential oils in food systems

and correlation with antimicrobial activities in food matrices have not been attempted. (Chen 2014).

Essential oils are widely used in the food industry. A nanoemulsion was developed to improve the functional performance of *Thymus capitatus* essential oil as natural food preservative. Results showed that the essential oil did not present any toxic effects and exhibited an enhancement antibacterial activity. The contact area of the essential oil was considerably increased and increased its antibacterial activity. The nanoencapsulation was performed using a high pressure micro-fluidizer. The continuous phase was composed of 1% aqueous sodium dodecylsulfate while the dispersed phase contained 70% essential oil and 30% soybean oil. The average droplets diameter was around 110 nm (Jemaa 2017).

Although essential oils show a good bioactivity in vitro, they can interact in foods with some components (fats, proteins, carbohydrates, NaCl) and be influenced by pH, thus many authors have reported that a significant effect of essential oil toward pathogenic microorganisms could be achieved in vivo by using higher amounts of oils. Obviously, a parallel can be made between the observed interactions of essential oils with the constituents of food and the interactions with food during the therapeutic ingestion of the same essential oils. Essential oils are lipophilic, thus they can easily enter cells, disrupt the membrane and/or permeabilize it (Perricone 2015). The most important signs of membrane permeabilization are the loss of ions and the reduction of potential, the collapse of proton pump and the depletion of ATP pool (Bakkali 2008).

In the food industry, essential oils are used mainly for their antibacterial effect. They need to be stabilized with emulsifying technologies to resist against evaporation and oxidation. Microemulsions and nanoemulsions are stabilized by additives such as surfactants that can be used in food. These emulsions are transparent and can be used also in beverage products, thereby decreasing the amount of the essential oils required (Sugumar 2016).

Typically, food matrices with hydrophobic food components, like proteins and lipids, can cause significant reductions in antimicrobial activities of essential oils. Despite numerous studies on antimicrobial activities of essential oils and speculation about food matrix interference, quantification of the solubility of essential oils in food systems and correlation with antimicrobial activities in food matrices have not been attempted. To improve the distribution of essential oils in food matrices and reduce interference by food components, various delivery systems, such as emulsions and biopolymer capsules have been studied to enhance the antimicrobial activity and reduce the usage level (Chen 2014).

5.1. Cooking application of essential oils

The benefits of cooking with essential oils are described on internet. ”You probably know that essential oils can be used in hundreds of different ways But few people realize that it is possible to safely and confidently use essential oils in your household kitchen. Cooking with essential oils can unlock a healthful and delicious experience that most people never consider”.

Essential oil in food. Retrieved 26 December 2018 from https://drjockers.com/benefits-cooking-essential-oils/

Essential oils are commonly used in cooking in salad dressings, marinades, baking, flavored vinegars, flavored oils, soups and on meat or fish after cooking. One or 2 drops of essential oils is all what is needed. It can be diluted in oils and should not be exposed to high heat. ForTasty combinations: add 5-7 drops of lemon or lavender essential oil to cakes or muffins.Grapefruit and lemon essential oil go rather well with fish; transform store bought ice cream into heavenly dessert with ginger and lime, spearmint and geranium, or rose and bergamot. Likewise, convert a boring plain steak into a gastronomic delight by adding a few drops of lemon, bergamot or thyme to the marinade” (Retrieved on 25 December 2018 from Supercharge your health https://drjockers.com/category/health-news/essential-oils/).
Considering that the main constituents of essential oils have unsaturated carbon chains, it is well known that they are susceptible to oxidation mediated by light or heat and that they evaporate quickly. It is therefore certainly recommended not to heat essential oils in the kitchen, but to add them at the end of the cooking procedure to the various dishes to be eaten warm.

Harevest of Monarda fistulosa L., L'Essencier, Icogne

6. Conclusion

Emulsions, encapsulations and complexations provide protection of essential oils against degradation and better bioavailability. They are well described in the literature and bring convincing results in cosmetics, pharmaceutical and food industries. Accompanied by additional intestinal permeability tests, we can expect interesting bioavailability improvements in the future.

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