Chapter 2

Bio-based Nanoemulsion Formulations Applicable in Agriculture, Medicine and Food Industry

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Abstract

Nanotechnology providing "a new dimension" accompanied with new properties conferred to many current materials is widely used for production of a new generation of agrochemicals, in medicine it enables improved drug bioavailability, reducing undesirable side effects, minimizing non-specific uptake and specific targeting to certain target cells, while in food industry it has great importance in food protection and biofortification of food with valuable ingredients. In bio-based nanoemulsions belonging to lipid nanocarriers plant oils used for oil phase, emulsifiers, biosurfactants, cosurfactants, targeting ligands on the surface of nanoemulsion (e.g., folate) or encapsulated active ingredients are of natural origin. The biocomponents of such nanoemulsions show low toxicity to living organisms, could protect encapsulated compounds for degradation, ensure their sustainable release and reduce the amount of active ingredient necessary for required effect. This chapter presents a comprehensive current overview of recent findings in the field of nanoemulsions and their utilization in agriculture and food industry, with the main emphasis on formulations encapsulating essential oils or plant extracts suitable as effective pesticide preparations as well as medicinal applications of bio-based nanoemulsions, where attention is paid to transdermal nanoemulsion formulations, the use of nanoemulsions in cancer therapy and for pulmonary and ocular drug delivery. Nanoemulsions formulated with natural emulsifiers, biosurfactants and biopolymers are presented and bio-based nanoemulsions of essential oils and their constituents as well as nanoemulsions with encapsulated vitamins, fatty acids and some bioactive compounds are discussed. Applications of nanoemulsions in edible coatings are outlined as well.

Key words: nanoemulsions, nanoformulations, nanocomposites, encapsulation, drugs, bioactive agents, foodstuffs, essential oils, packaging materials

2.1 Introduction

Nanotechnology is a fast growing field that provides for the development of materials that have new dimensions, novel properties, and a broader array of applications (e.g., (Achari and Kowshik 2018; Agarwal et al. 2018; Jampílek and Kráľová 2015a, 2017a,b; 2018a,b; Prasad et al. 2017a,b; Sekhon 2014; Ventola 2017). It is regarded as one of the key technologies of the 21st century. U.S. National Nanotechnology Initiative defines nanoparticles (NPs) in the range 1–100 nm (National Nanotechnology Initiative 2008). NPs and nanoformulations can be prepared from both inorganic and organic materials (e.g., Bhushan et al. 2014; Singh et al. 2015; Jampílek and Kráľová 2018a; Pisarčík et al. 2018). As mentioned above, nanoscale materials change properties and behavior of all materials and thus a variety of industrial, agricultural, pharmaceutical and

medical products have been improved and innovated in such a way (e.g., Dolez 2015; Patra et al. 2018; Sekhon 2014).

In modern agriculture, the main form of control of diseases and agricultural pests is performed using agrochemicals. However, extensive and intensive use of these compounds has resulted in environmental contamination, development of resistance in some species, decreased food safety, and side effects in non-target organisms (Aktar et al. 2009; Fountain and Wratten 2013; Prasad et al. 2014; 2017a). To address these issues, the development of nano-based pesticides and also the utilization of bio-based pesticides has become an important research tool (Campos et al. 2016, 2018; Hayles et al. 2017; Hemraj 2017; Kah et al. 2018; Jampílek and Kráľová 2015a, 2017a, 2018c, 2019a) and the application of nanofertilizers results in increased nutrient use efficiency in crop production (Achari and Kowshik 2018; Jampílek and Kráľová 2017c; Raliya et al. 2018). Nanoemulsions (NEs) showing desirable physico-chemical characteristics have been extensively studied as carriers for pesticide delivery (Wang et al. 2007; Knowles 2008; Hayles et al. 2017; Hazra et al. 2017).

However, nanotechnology is increasingly being applied also in medicine, in theranostic and drug delivery (Prasad et al. 2016; 2017b). By encapsulation into nanoformulations sustainable release of drugs as well as reduction of the required drug amount could be obtained and nanomaterials represent also an alternative approach to treating and mitigating infections caused by resistant bacteria (e.g., Jampílek et al. 2015b; Jampílek and Kráľová 2017b, 2018a, 2019b,c; Pentak et al. 2016; Patra et al. 2018; Prasad M et al. 2018).

In the food sector the nanotechnologies are used for food protection, including nanocomposites for protection of fruits, vegetables, cheese, dairy products, meat or fish, in smart active packaging, responsive packaging or edible coatings and like that significantly contribute to enhanced food quality. Moreover, they found wide application also as nanosensors (e.g., Chellaram et al. 2014; Jampílek and Kráľová 2015a, 2018b; Malhotra et al. 2014; Mihindukulasuriya and Lim 2014; Singh et al. 2017a).

For preparation of bio-based NEs many compounds of natural origin, including encapsulated active ingredients (e.g., essential oils; EOs), but also plant oils for NE oil phase (e.g., palm oil, rapeseed oil, sunflower oil etc.) (e.g., Raviadaran et al. 2018; Kaci et al. 2018; Abdou et al. 2018), emulsifiers, biosurfactants or cosurfactants (e.g., *Quillaja* saponin, phospholipids, lecithin, gum arabic, pectin, whey protein, lactoferrin, lactoferrin/alginate) (Bai et al. 2016; McClements and Gumus 2016; Ozturk et al. 2014, 2015; Liu et al. 2017; Verma et al. 2016; Artiga-Artigas et al. 2018; Zhao et al. 2018a; Pinheiro et al. 2016), or targeting ligands on the surface of NE such as folate (Liu et al. 2017; Ganta et al. 2016; Afzal et al. 2016a) increasing drug bioavailability, reducing undesirable side effects, minimizing non-specific uptake and thus allowing specific targeting to certain target cells are used. Targeting technology usually utilizes the nanocarrier functionalization, which can be surface modification (e.g., Attia et al. 2017; Liu et al. 2017) and/or ligand grafting (e.g., Geng et al. 2016). Chitosan (CS)-based NE coatings are used to enhance mucoadhesive properties (Fachel et al. 2018; Mendes et al. 2017; Kumar et al. 2009) as well as antimicrobial activity of these nanoformulations (Marei et al. 2018; Severino et al. 2014, 2015), and also pectin, sodium caseinate or carrageenan (Abdou et al. 2018; Qian and McClements 2011; Alarcon-Alarcon et al. 2018) are used as NE coatings.

This chapter is focused on the use of NEs in agriculture, with the main emphasis on formulations encapsulating EOs or plant extracts suitable as effective pesticide preparations as well as medicinal applications of bio-based NEs, where attention is paid to transdermal NE formulations, the use of NEs in cancer therapy and for pulmonary and ocular drug delivery. NEs formulated with natural emulsifiers, biosurfactants and biopolymers are presented and bio-based NEs of EOs and their constituents as well as NEs with encapsulated vitamins, fatty acids and some bioactive compounds are discussed. Applications of NEs in edible coatings are outlined as well.

2.2 Nanoemulsions and methods of their preparations

Nanoemulsions (NEs) are biphasic dispersions of two immiscible liquids: either water in oil (W/O) or oil in water (O/W) droplets stabilized by an amphiphilic surfactant, whereby very small emulsion droplets (generally oil droplets in water) with sizes in the order of 100 nm (usually >500 nm) and occurring from a thermodynamic point of view in a non-equilibrium state, are characterized by slow kinetics of destabilization and therefore they could be considered as kinetically stable. Small size of NEs results in convenient features such as high surface area per unit volume, robust stability, optically transparent appearance, and tunable rheology (Anton and Vandamme 2011; Gupta et al. 2016; Singh et al. 2017b; Sabry and Ragaei 2018). Very small size of NEs pronouncedly contributes to the prevention of droplet flocculation and coalescence and thus, the destabilizing process is governed alone by the Ostwald ripening (Anton and Vandamme 2011). As the destabilization of NE occurs due to the change in the droplet size by Ostwald ripening, surface functionalization of NEs could be used to stabilize the O/W interface during emulsification (Quadir et al. 2016). NEs prepared using biocompatible and biodegradable constituents could be used in medicine and food industry for drug/active ingredient encapsulation and sustained and controlled release of encapsulated compounds also belong to their advantages.
On the other hand, according to the IUPAC definition, the microemulsion (ME) is "dispersion made of water, oil, and surfactant(s) that is an isotropic and thermodynamically stable system with dispersed domain diameter varying approximately from 1 to 100 nm, usually from 10 to 50 nm, whereby the term "oil" refers to any water-insoluble liquid (Slomkowski et al. 2011). In general, NEs could be formulated using so-called "high-energy" methods that utilize specific devices (e.g., ultrasound generators or high pressure homogenizers) supplying enough energy to increase the W/O interfacial area for generating nanoscale droplets or by „low-energy" methods, in which spontaneous emulsification without requiring any device or energy generate nanoscale droplets (e.g., Jaiswal et al. 2015; Håkansson and Rayner 2018; Hadžiabdic et al. 2017).
The high pressure homogenization, microfluidization, sonication or ultrasonic homogenization, jet disperser high-amplitude ultrasonic method or membrane emulsification belong to the high-energy methods used for preparation of NEs. The high-energy methods are designed to supply the energy required for emulsification by subjecting it to a disruptive hydrodynamic stress, that is, laminar or turbulent shear or cavitations (e.g., Håkansson and Rayner 2018; Hadžiabdic et al. 2017). For example, a dual-channel microfluidization is a suitable method to fabricate fine NEs with high oil loading levels, which may be advantageous for many commercial applications, while the single-channel method was found to be effective only at producing NEs at relatively low oil concentrations (10%) (Bai and Clements 2016). In β-carotene NEs prepared by microfluidization technique droplet size decreased from 416.0 to 97.2 nm with increasing microfluidization pressure, number of cycles, and emulsifier concentration and as the optimum conditions for fabricating such NEs homogenization pressure of 120 MPa and 3 cycles were estimated (Jo and Kwon 2014). Abbas et al. (2013) outlined the principles and production technology of high-intensity ultrasound, analyzed the role of acoustic cavitation in the preparation of food-grade O/W NEs discussed technical hurdles, issues and future prospects of this technology.
Low-energy transitional emulsification methods to prepare NEs based on phase transitions of nonionic surfactants (PEGylated surfactants) related to a sudden change in their relative solubility in the oily phase and aqueous phases was overviewed by Anton et al. (2018). Spontaneous emulsification is a low-energy method that simply involves addition of an organic phase (oil + surfactant) into an aqueous phase and the produced droplet size is affected by surfactant-to-oil ratio, surfactant type, surfactant location, and oil type (Komaiko and McClements 2016). The catastrophic phase inversion method for fabrication of NE is based on gradually diluting, under mild flow conditions, one liquid (such as water) with another immiscible liquid (such as oil) until phase inversion occurs and a NE is formed (e.g., O/W) that could be used to encapsulate many active compounds (Perazzo and Preziosi 2018).

2.3 Nanoemulsions applicable in agriculture

The primary object of preparing chemical pesticide colloids is significantly increase the apparent solubility of these molecules in water and consequently the delivery of the active compound homogeneously to the pests and/or plants. However, recent research has shown that the production of these colloids can also improve other properties of pesticides, such as bioavailability, increased physico-chemical stability and promote sustained release (Bhattacharyya et al. 2016).

Pesticides formulated with NEs use less organic solvents when compared with conventional formulations (emulsifiable concentrate) (Chin et al. 2012) and also, have lower surfactant concentration (between 3–10%) than microemulsions (20% or higher) (McClements 2012). In comparison to the emulsions the advantages of the NEs due to the small droplet size are the greater spreadability, wettability and superior mechanical stability (McClements 2012). Consequently, NEs incorporating pesticides settle evenly on the leaves of plants. Some studies have shown that NE improves the solubility of poorly water-soluble pesticides, resulting in the increasing of bioactivity of the pesticides in comparison with conventional pesticides (Leng et al. 2014; Wang et al. 2017).

Using a *Quillaja* saponin as a natural surfactant Kumari et al. (2018) prepared and characterized thymol NE. The authors tested the antibacterial activity of the NE against *Xanthomonas axonopodis* pv.*glycine*, which is the organism responsible for bacterial pustule disease in soybean. The most stable NE was produced with fifty minutes of sonication and resulted in a NE with mean diameter 274±2 nm, polydispersity index (PDI) 0.1 and zeta potential -31 mV. Thymol NE showed strong antibacterial activity, and no bacterial colony was observed in the concentration range of 0.02–0.06 (v/v) of NE as compared to control and thymol and saponin. The incidence of the disease was evaluated *in vivo* and the results showed that the control plants and plants treated with thymol and saponin alone presented a higher disease incidence (64–78%), while lower disease incidence (3.3–29%) was observed in plants treated with thymol NE. Treatment with NE also resulted in enhancements of plant growth.

In the study of Lim et al. (2013) the authors prepared and characterized a water-soluble herbicide formulation based on NEs of glyphosate isopropylamine. The herbicidal activity was evaluated against three weeds: *Asystasia gangetica*, *Diodia ocimifolia* and *Paspalum conjugatum*. The authors found that the glyphosate NEs showed a lower spray deposition in all species when compared to a commercial formulation (Roundup®). However, after 14 days of the treatment the injury rates of the weeds treated with NE were similar to those observed with plants that were treated with commercial formulation. The similar herbicidal activities of NE and the commercial formulation, even with the lower NE deposition, could be attributed to potentiation of the biological activity when glyphosate was formulated as NE.

In another paper, Du et al. (2016) described the preparation and characterization of O/W NEs using laurate as oily phase and a mixture of two surfactants, alkyl polyglycoside (AL) and polyoxyethylene 3-lauryl ether (PLE). In order to evaluate the potential application of the NEs a model insoluble molecule, β-cypermethrin, was incorporated into the NEs. Two NEs were analyzed, the first one containing laurate/AL:PLE(6:4)/water in a ratio 10:5:85 and in the second one this ratio was 20:6:74. NE prepared with the lowest laurate concentration showed lower mean diameter (~110 nm) in comparison with NE prepared with higher concentration of laurate (~200 nm). However, in both cases there were no significant changes in droplet size between the NEs prepared with and without β-cypermethrin. Even after dilution the β-cypermethrin the NE remained as single-phase and homogeneous. After dilution an increase in droplet size was observed. As consequence, diluted NE showed excellent wetting and spreading properties on the hydrophobic surface.

Badawy et al. (2017) prepared O/W NE with an insecticide (diazinon) using Tween or lecithin as surfactants. In the prepared optimized NE the dependent variables were droplet size, PDI, dynamic viscosity and pH. NE prepared using synthetic surfactant (Tween) showed a size droplet varying from 30 to 138 nm and PDI values from 0.084 to 0.256. The NEs prepared using natural surfactant (lecithin) showed a broader range of droplet size varying from 56.2 to 920.2 nm and also broader range of PDI values (0.122–0.946). Diazinon NE prepared using Tween showed low

viscosity ranging from 2.33 to 21.33 cP, whereas viscosity of lecithin NE incorporating diazinon were higher (55–1039.33 cP). Both NEs prepared with natural or synthetic surfactant showed an acid pH value. In another study aiming to NEs applications in agriculture, Zhao et al. (2017) developed and characterized a positive charged O/W NE as a carrier system for lambda-cyhalothrin and evaluated the influence of addition of externally ionic liquids on Z-average, size distribution, zeta potential, viscosity and stability of the NEs. The measurement of contact angles of NEs on wheat leaves (*Triticum aestivum*) was evaluated. The zeta potential of the NE was affected by the addition of ionic liquids with different alkyl chain length. Increases in alkyl chain length resulted in a change of droplet charge from negative to positive. The droplet size showed no increases in diameter after 90 days of storage and NE exhibited a non-Newtonian fluid behavior. NE showed a tough adsorption on negative surface decreasing the contact angle on wheat leaves. The addition of ionic liquids provided an increase in the stability due to electrostatic repulsion and the NE could be considered as a potential carrier system for agrochemicals.

Choupanian et al. (2017) studied the preparation and characterization of neem oil NE and evaluated the increase in the NE stability by addition of two non-ionic surfactants (naturally based polysorbate and alkylpolyglucoside). The biological activity of neem oil NE was evaluated against two important pests of stored products: *Sitophilus oryzae* (L.) and *Tribolium castaneum* (Herbst). All NEs showed a droplet size ranging from 200 to 600 nm and the formulation, that showed higher ratio of non-ionic surfactants, had smaller droplet size in comparison to the formulations showing the same composition of surfactants, however with lower concentration. The addition of non-ionic surfactants resulted in increases in viscosity of the NE. Both pests treated with 1% of NE showed 100% of mortality after two days of treatment, except for the NE with higher droplet size (507 nm) causing 85 and 74% mortality of *S. oryzae* and *T. castaneum*, respectively. However, all NEs showed more toxic effects against both pests compared with free neem oil and Neemix®.

Díaz-Blancas et al. (2016) prepared O/W NEs entrapping tebuconazole using non-ionic surfactant (Tween 80) or AG54, which is a surfactant composed by a mixture of non-ionic and anionic amphiphilic components. According to a pseudo-ternary diagram, the phase equilibrium area was achieved in the range of 0.49–0.90, 0.01–0.23, and 0.07–0.49 of organic phase, aqueous phase, and surfactant, respectively. The viscosity of both NEs depended on aqueous phase percentage and showed the same behavior. When the concentration of the aqueous phase increased from 4 to 30 wt%, a 4-fold decrease in the viscosity was observed, whereas increase in aqueous phase concentration from 30 to 50 wt% resulted in viscosity increase, however, NE prepared with Tween 80 showed higher viscosity than NE fabricated with AG54. The droplet size of the NE containing Tween 80 was 9±1 nm and the size remained constant with the increase of concentration in aqueous phase from 1 to 50 wt%. In contrast, NE produced with AG54 showed a strong dependence on the aqueous phase concentration up to 20 wt%. However, further increases in the percentage of the aqueous phase did not influence the size droplet that remained around 250 nm.

Hazrati et al. (2017) studied O/W NE containing *Satureja hortensis* essential oil (EO) and evaluated the herbicidal activity of the NE against worldwide weeds *Amaranthus retroflexus* and *Chenopodium album.* The NE showed a droplet size of 92.7±2.6 nm and PDI 0.29±0.01 and after 30 days of storage an increase of mean diameter and a decrease in PDI was observed. Under laboratory conditions the germination percentage showed a dose-dependent response and the best germination inhibition was observed for the concentration 800 µL/L NE. In this assay, the root elongation was more affected in comparison with shoot elongation. In greenhouse assays a decrease in growth of the plants in a dose-dependent manner was observed as well. In addition, a decrease in chlorophyll content and increase in relative in electrolyte leakage 5 days after the treatment was estimated, which could be attributed to cell membrane disruption and increased membrane permeability. This NE presented herbicidal activity against weeds due to the presence of carvacrol that is a phenolic monoterpene showing strong phytotoxic effects.

Feng et al. (2016) evaluated the effect of adding the aqueous phase to the organic phase and vice versa, as well as the initial location of the surfactant (organic phase or aqueous phase) on the stability of NE using β-cypermethrin as pesticide model. According to the authors the NE stability depended strongly on the emulsification process. NEs, in which the emulsifier agent was diluted in organic phase showed higher stability than NEs, in which it was diluted in aqueous phase. In addition, the most stable NE was prepared by adding the organic phase containing the emulsifier in the aqueous phase. This NE showed a droplet size of 166 nm and PDI of 0.16.
Mossa et al. (2017) fabricated NEs of camphor EO and evaluated their insecticide activity against *Sitophilus granaries*. NEs were produced with fixed concentration of camphor oil (5%), different ratios of Tween 20 (w/w) and different sonication time. Optimized NEs were achieved at a ratio 1:1.5 of Tween 20 : camphor EO and 40 minutes of sonication, showing a droplet size of 99.0±0.605 nm and remained unchanged during three months of storage. Both camphor EO and NE showed insecticidal activity against *S. granaries* in a dose-dependent manner. After 72 h of exposure to the highest concentrations of the NE tested (250 and 300 μg/g) 100% of insect mortality and reduction in the progeny (98 and 100%) was observed and higher concentration of the free EO was necessary to reach the same effect. The estimated LC_{50} for EO and NE were 282.01 μg/g and 181.49 μg/g, respectively. The insect mortality caused by EO was increased by 36.5% when this oil was incorporated into the NE.
In addition, Fernandes et al. (2014) developed a NE with an extract consisting of the apolar fraction from fruit extract of *Manilkara subsericea* and evaluated its insecticidal activity against *Dysdercus peruvianus*. The best oil phase was found to be octyldodecyl myristate that was able to solubilize equal amount of apolar extract (1:1 w/w). Optimized emulsion was composed of the apolar extract (5%), surfactants (5%), octyldodecyl myristate (5%) and water phase (85%). The NE without extract showed a droplet size of 57±0.3 nm and zeta potential of -59.6 ±4.1 mV, while the NE containing the extract showed an increase in mean diameter (155.2±3.8 nm) and a decreased zeta potential value (-47.4±3.2 mV). The mortality of the insects treated with NE containing the extract, that started in the first day reached 12.23±0.58%, after 30 days of exposure was enhanced to 44.43±6.66%. It could be mentioned that NE containing extract did not induce effect against acetylcholinesterase or mortality in mice.
In order to improve the permeability and efficiency of delivery of antibacterial (ampicillin) into the citrus phloem by foliar spray Yang et al. (2015) designed a NE using eight adjuvants. Among the adjuvants tested, Brij 35 showed the highest increases (3.33-fold) in the cuticular permeability when compared with control (water). Two O/W NEs were prepared with different physicochemical properties; however, both formulations showed good thermodynamic stability. One NE showed droplet size of 5.26±0.04 nm and pH value 7.76±0.03 (NE-1) and another one had higher droplet size (94±1.48 nm) and higher pH value (8.31±0.05) (NE-2). After addition of the adjuvant (Brij 35) to both NEs a laboratory assay with *Bacillus subtilis* was performed in order to evaluate the antibacterial activity. The NEs showed higher inhibitory zone diameters of 5.75 and 6.6 mm for NE-1 and NE-2, respectively in comparison with Brij 35 alone (4.34 mm) and free ampicillin (2.83 mm). In addition, *in vivo* assays also showed that the NEs were more efficient at suppressing or eliminating Las bacterium when compared with free ampicillin and Brij 35 alone.
Ali et al. (2017) developed NEs containing neem and cintronella oil using a method of low energy spontaneous emulsification. Antifungal activity of NEs was evaluated against two phytopathogenic fungi *Rhizoctonia solani* and *Scletotium rolfsii*. Optimized primary emulsion for both oils was achieved using the ratio of oil, surfactant and water of 0.50:1:8.50. This primary emulsion was employed to make neem NE with diverse amounts of citronella oil (0.5–5%) or citronella oil NE with diverse amounts of neem oil (0.5-5%). Neem NEs with different percentage of citronella oil showed a droplet size varying between 11.23±3.86 nm to 17.80±4.52 nm, whereas citronella oil with diverse amounts of neem oil showed a droplet size varying between 8.12±2.80 nm to 12.04±3.74 nm. *In vitro* antifungal activity of the different NEs against *R. solani* and *S. rolfsii* was screened by poisoned food method. Neem NE with the highest percentage of citronella oil and citronella NE with the highest percentage of neem oil showed the

best antifungal activity against the both fungi tested. The estimated LC_{50} related to *R. solani* were 13.67 and 25.64 mg/L and those related to *S. rolfsii* were 14.71 and 20.88 mg/L respectively for neem NE and citronella NE, respectively.

Liu et al. (2011) studied O/W NEs composed of different mixture of non-ionic surfactant polyoxyethyene 3-lauryl ether ($C_{12}E_3$) and anionic surfactant dipotassium monododecylphosphate (MAPK) containing the insecticide bifenthrin. According to the authors the most stable emulsion was achieved with a mixed ratio of 6:4 (MAPK:$C_{12}E_3$) and 10 wt% surfactant mixture. The NE showed a droplet size of 200.7 nm that increased after 180 days of storage to 218.6 nm but phase separation was not observed. Pant et al. (2014) prepared NEs of eucalyptus oil and evaluated the potentiation of their insecticidal activity by addition of the aqueous filtrate of *Pongamia glabra* and *Jatropha curcas.* Insecticidal activity was estimated against *Tribolium castaneum* that is an important pest of stored grains. Four formulations, all containing the same composition and the same concentration of eucalyptus oil (10% w/w) were prepared, whereby the only component that varied was the aqueous filtrate concentration of karanja and jatropha (0, 20, 49 and 60 %). The droplet size of the NEs decreased with increasing concentration of the aqueous filtrate in the formulation. NE produced only with water as continuous phase showed the highest PDI (0.8), while the NE with 20% of aqueous filtrate showed PDI of 0.113, which increased to 0.278 at the highest concentration of aqueous filtrate utilized. The percentage of insecticidal activity of *T. castaneum* did not show significant difference among all formulations tested; however, it was observed a significant decrease in the value of LC_{50} from 5.49 mg/L estimated for the NE without plant aqueous filtrate to 0.1646 mg/L for the NE with 60% of aqueous filtrate. In addition, the volatilization of the eucalyptus oil was stabilized in the NE with aqueous filtrate.

Sharma et al. (2018) evaluated NEs prepared using non-ionic surfactants and containing a mixture of two EOs, clove oil and lemongrass oil, for antifungal activity against *Fusarium oxysporum* f.sp. *lycopersici* (FOL). Optimized formulation contained 5% of a blend of clove oil and lemongrass oil (1:1), 10% of surfactant mixture (Tween 20: CoE-40, 7:3), 5% propylene glycol and 80% water. This NE showed droplet size 76.73±4.8 nm, PDI 0.207±0.02 and viscosity 26.9±1.9 cP. Such NE was more efficient (48.5% more fungistatic activity) in inhibiting the mycelial growth (MIC 4000 mg/L) in comparison with free oil mixture (MIC 7000 mg/L). In addition, NE showed more pronounced fungicidal activity (5000 mg/L) than free oil mixture (9000 mg/L) against FOL, whereby the nanoemulsion disrupted the membrane integrity of FOL.

Hashem et al. (2018) developed a NE containing *Pimpinella anisum* L. EO and evaluated its insecticidal activities against *Tribollium castaneum* adults and progeny. The NE showed a droplet size of 198.9 nm, PDI 0.303, zeta potential of -25.4 mV and low viscosity 0.8872 cP. Adult mortality increased proportionally with increasing NE concentrations as well as time of exposure, while the number of progeny and grain weight showed gradual decrease. After 12 hours there was 81.33 ±0.08% of adult mortality and reduction of 70.85% if the progeny when exposed to 10% NE and the LC_{50} value after 72 hours of exposure was 9.84%. The NE adhered to different parts of the insect body, such as, head, thorax, abdomen, elytra, mouth and legs. In addition, the NE caused a distinct kind of alteration in the midgut cells of the insects. Abd-Elsalam and Khokhlov (2015) prepared eugenol NE using Tween 20, a non-ionic surfactant, and water as continuous water phase and evaluated its antifungal activities *in vitro* and *in vivo* against *Fusarium oxysporum* f. sp. *Vasinfectum* (FOV) isolates. Eugenol NE showed a droplet size of 80 nm, spherical shape and no increases in droplet size after 30 days of storage at room temperature (25 °C). *In vitro* antifungal activity (zone inhibition) showed that among the four FOV tested the NE was more efficient against DQO86833 (5 cm) and AY264267 (4.5 cm) at application of 2% NE, whereas treatment with 5%, NE inhibited the mycelial growth of all FOV isolates. Fungal morphology was also affected by the NE, and reduction in the size and number of conidiospores as well as reduction in hyphae pigmentation were observed.

As a summary, in literature there are many examples of systems with potential to be used in agriculture, however, a lot of work to become all initiatives in products to be used in crop protection.

2.4 Nanoemulsions applicable in medicine

NEs as stabilized heterogeneous systems of two immiscible liquids have a great potential in various biomedical applications; especially they are very attractive for drug delivery. Encapsulation in particular lipophilic drugs leads to the formation of therapeutic nanoformulations providing modification of bioavailability, alternative administration routes, release of drugs and, thus, a reduction of the required drug amount (e.g., Jampílek et al. 2015b; Jampílek and Kráľová 2017b, 2018a, 2019b,c; Pentak et al. 2016; Patra et al. 2018; Prasad et al. 2017b; Prasad M et al. 2018; Tayeb and Sainsbury 2018).

2.4.1 Transdermal nanoemulsion formulations

Drugs with low oral bioavailability due to the first pass metabolism are good candidates for transdermal delivery. Transdermal permeation of majority drugs is hindered by the upper layer of the epidermis (*stratum corneum*), therefore for topical delivery of drugs chemical permeation enhancers that are able to make the *stratum corneum* more permeable for drugs and reduce the primary skin barrier by different mechanisms are used. In addition, physical methods (e.g., sonophoresis, iontophoresis, electroporation, microneedles, etc.) can be used to increase permeability of drugs (Jampílek and Brychtová, 2012). For enhancing epidermal and dermal drug deposition also nanoscale drug delivery systems, including NEs, are widely applied (Iqbal, et al. 2018). Although the skin represents a natural physical barrier against particle penetration, the therapeutic NPs could be delivered especially in diseased skin and to the openings of hair follicles (Prow et al. 2011) and good candidates for transdermal delivery are drugs with low oral bioavailability due to the first pass metabolism. It is advantageous that NEs are vehicles acting also as transdermal permeation enhancers without utilizing additional permeation enhancers (Shakeel et al. 2010).

The progressive advancement in the delivery of drugs via NE with special reference to the dermal and transdermal administration and the most suitable semisolid dosage forms for the particular type of NEs (O/W, W/O and others), including effects of particle size and zeta potential on the delivery of drugs through dermal or transdermal route was overviewed by Rai et al. (2018). Low viscosity of NEs that might be unsuitable for topical application could be overcome by hydrogel-thickened NEs using thickening polymer, e.g. CS (Barradas et al. 2017). Challenges and future prospects of NEs as a drug delivery system were presented by Yukuyama et al. (2017). Applications of NEs in the field of dermatology highlighting the advantages over the other dermatological therapies connected with increased contact surface area by the particle size, which leads to increased drug efficacy were overviewed by de Souza et al. (2018). For example, Salim et al. (2016) discussed the potential of drug-loaded NEs for the treatment of psoriasis to achieve better efficacy and eliminate side effects and noted that the delivery and penetration of a drug through the psoriasis skin layer could be enhanced by a small droplet size. Nastiti et al. (2018) in their review paper focused their attention on the composition and characterization of MEs and NEs for topical and transdermal delivery and the mechanism of skin delivery across *stratum corneum* and via hair follicles.

Nanoemulgels that are basically O/W NEs gelled with the use of some gelling agent in it, in which the gel phase in the formulation is nongreasy and stabilizes the formulation through reduction in surface as well as interfacial tension could be considered as a novel transdermal delivery system that is able to overcome poor oral bioavailability of drugs, more specifically target to the site of action, can avoid first-pass metabolism and relieve the user from gastric/systemic incompatibilities (Choudhury et al. 2017). In nanoemulgels the NE containing drug is incorporated into a gel base. Lipophilic drugs could be easily incorporated and the skin permeability of the incorporated drugs can be enhanced in several folds due to the finely distributed droplets of NE phase resulting in notably improved pharmacokinetic and pharmacodynamic profiles of the lipophilic drugs. Consequently, nanoemulgel formulations

could be considered as potential and promising candidates for topical delivery of lipophilic drugs in the future (Sengupta and Chatterjee 2017). A review paper of Pawar and Babu (2014) is devoted to various lipid materials (vegetable oils, fatty acids, fatty alcohols, medium chain glycerides, and fatty acid esters) used in the preparation of NEs for topical and transdermal drug delivery.

Integral NEs with particle size of 80 nm can diffuse into but not penetrate the viable epidermis, however, they can efficiently fill the whole hair follicle canals and reach as deep as 588 μm underneath the dermal surfaces and the "cargos" released from the NEs diffuse into the surrounding dermal tissues. On the other hand, NEs with mean particle size of 500 nm, cannot penetrate the *stratum corneum* and can only migrate along the hair follicle canals, while NEs with median size, e.g. 200 nm show moderate transdermal permeation effect (Su et al. 2017). Capsaicin O/W NEs with droplet sizes 20–62 nm were reported to permeate all skin layers from the *stratum corneum* to the dermis (Kim et al. 2014a).

Permeation flux of antifungal drug fluconazole from optimized drug-loaded olive oil NEs through artificial skin was approximately three fold higher than the control (Ansaril et al. 2017). A testosterone transdermal delivery system developed using a palm oil base (HAMIN™) with particle sizes 97–774.0 nm was tested using *in vivo* skin permeability test and it was found that testosterone was well absorbed with a mean C_{max} and T_{max} of 60.94 ng/mL and 2.29 h after *in vivo* application on rabbit skin indicating that such nanoformulation could have great potential for topical delivery of testosterone (Haron et al. 2015). The optimized clove oil based olmesartan NE (droplet size of 53.11±3.13 nm, PDI 0.335±0.008) showing a 1.23-fold increase in the bioavailability compared with oral formulation of drug due to better permeation through rat skin could be used as an antihypertensive dosage form for effective transdermal delivery of olmesartan (Aqil et al. 2016). O/W NEs containing the skin penetration enhancer oleic acid or eucalyptol as oil pronouncedly enhanced the skin penetration of encapsulated caffeine and naproxen compared to their aqueous control solutions. Caffeine maximum flux enhancement was connected with a synergistic increase in both caffeine *stratum corneum* solubility and skin diffusivity, while increased solubility in the *stratum corneum* was the dominant determinant for higher naproxen fluxes (Abd et al. 2016). Transdermal NE formed of 2% *Foeniculum vulgare* Mill. EO, 5.6% oleic acid, 68% S_{mix} (1:1) and distilled water showed a high potential of reducing plasma glucose levels in rats that continued for 7-days after a single topical application of a dose of 120 mg/kg of fennel EO, bringing glucose to normal levels in diabetic rats (Mostafa, et al. 2015a). O/W NEs containing minoxidil, an antihypertensive vasodilator, and the skin penetration enhancer oleic acid or eucalyptol as oil phases pronouncedly enhanced drug permeation through skin compared with control solutions. Minoxidil retention in the *stratum corneum* and deeper skin layers was promoted to higher extent with eucalyptol NEs, while oleic acid formulations gave the greatest hair follicle penetration. The increases in both minoxidil *stratum corneum* solubility and skin diffusivity in both nanoemulsion systems were reflected in drug maximum flux enhancement connected with enhanced fluidity and disruption of *stratum corneum* lipids (Abd et al. 2018). NEs containing isoflavone-rich soybean extracts that are considered as promising skin antiaging products due to their antioxidant activity could be applied as suitable topical formulations to protect skin from UVA/UVB oxidative damage (Back et al. 2018). Antioxidant hydrogels containing an *Achyrocline satureioides* extract-loaded NEs aimed at topical application were found to be suitable to protect the porcine ear skin against oxidative stress generated by UVA/UVB light (Balestrin et al. 2016). Brownlow et al. (2015) developed vitamin E-enriched NE vehicles loaded with genistein for chemoprevention against UVB-induced skin damage showing enhanced dermal delivery of the drug. Also Nam et al. (2018) developed W/O NE (diameter of <5 nm) that contained nitric oxide (NO) by mixing surfactant with vitamin E antioxidant body oil (Product No. 04800, Cococare, Dover, NJ) and $NaNO_2$ solutions. After spreading of this NEs with NO on penis skin of the middle aged dogs, blood NOx concentration in the penis increased, resulting in penile erection without any notable topical and systemic side effects, suggesting that such W/O NEs could be used in non-invasive

medication for patients suffering in erectile dysfunction with low response to phophodiesterase type 5 (PDE5) inhibitors such as Viagra or Cialis.

Formulations of hydrogels containing negatively or positively charged Copaiba oil NEs exhibited anti-inflammatory effects, which was reflected in mouse ear edema (69 and 67%) and rat paw edema inhibition (32 and 72%) and decrease of inflammatory factors, such as dermis and epidermis hyperplasia and inflammatory cells infiltration in histological cuts were estimated as well (Lucca et al. 2018). Skin permeation with the positively charged Copaiba oil NEs increased threefold the retention of the major component in copaiba oil, β-caryophyllene, in the epidermis, and also in the receptor fluid compared to the negatively charged NEs (Lucca et al. 2017). Coffee oil–algae oil-based NEs with a particle size of 30 nm, zeta potential -72.72 mV, and 100% encapsulation efficiency (EE) of docosahexaenoic acid (an important component of algae oil) applied at dose of 0.1% efficiently mitigated trans-epidermal water loss, skin erythema, melanin formation, and subcutaneous blood flow in animal experiments and were found to inhibit the growth of melanoma cells B16-F10 (IC_{50}: 26.5 μg/mL) and arrest the cell cycle G_2/M phase, whereby the apoptosis pathway of melanoma cells may involve both mitochondria and death receptor (Yang et al. 2017).

Transdermal administration of nanogel based on optimized catechin NEs showed sustained release profile of catechin and enhanced photoprotection potential due to its improved permeability as well as bioavailability compared to the conventional gel and it could represent an effective strategy for decreasing UV-induced oxidative damage in the skin tissues (Harwansh et al. 2016). Natural pentacyclic triterpenes-loaded NEs showed greater ability to inhibit inflammation than NEs loaded with the synthetic mixture of triterpenes (Alvarado et al. 2015).

NEs of CS oleate encapsulating α-tocopherol with particle size of 220 nm were reported to be suitable for topical application in wound healing (Bonferoni et al. 2018). Astaxanthin (ASX)-loaded carboxymethyl CS functionalized NE formulation with spherical droplets showing mean diameter >100 nm and a small negative surface charge exhibited higher ASX chemical stability and skin permeability than ASX NEs and ASX solution and were characterized with low cytotoxicity (Hong et al. 2017).

Genistein-loaded cationic NEs (mean droplet size of ca. 200−300 nm) prepared by spontaneous emulsification and using hydroxyethyl cellulose as a thickening agent (at 3%) showed considerable increase of drug retention in mucosa compared to the genistein propylene glycol solution, and exhibited antiherpetic activity *in vitro* against herpes simplex virus 1 (HSV-1, strain 29R) (Argenta et al. 2016). Factorial design applied to the optimization of lipid composition of topical antiherpetic NEs containing isoflavone genistein was presented by Argenta et al. (2014).

The 10,11-methylenedioxycamptothecin loaded hyaluronic acid (HA) NEs were reported to perform desirable skin permeable capacity across human keloid skin, whereby the drug was transferred directly to keloid lesion area. The growth-inhibitory effect was further clarified upon cell cycle regulation, which arrested cells at G_1/S and prevented them entry into mitosis (Gao et al. 2014).

NEs with co-encapsulated C6 ceramide (0.35%) and paclitaxel (0.50%) containing tributyrin delivered 2- and 2.4-fold more paclitaxel into viable skin layers of porcine skin *in vitro* at 4 and 8 h post-application than the MEs, and 1.9-fold more C6 ceramide at 8 h, whereby the drugs were co-localized mainly in the epidermis. The EC_{50} values related to melanoma cells viability estimated for individually encapsulated paclitaxel and ceramide in NEs were 4- and 13-fold lower (ceramide) than for unencapsulated formulation and at co-encapsulation of both active ingredients synergic effect was observed, because further decrease of EC_{50} by 2.5−4.5-fold was estimated, and calculated combination index also indicated a synergistic effect. Topical application of NEs on 3D bioengineered melanoma models for 48 h stimulated marked epidermis destruction and only few cells remained in this layer (Carvalho et al. 2017).

The olein-based β-D-glucan-loaded NE prepared using ultrasound exhibited higher antioxidant activity as compared to free antioxidant β-D-glucan (Alzorqi et al. 2016). In sulpiride ME formulations containing glycerylmonooleate, Labrafil and Avocado as oily phases drug solubility increased to 43.35 mg/mL with drug content >97% and based on pharmacodynamic performance

and antipsychotic activity of sulpiride this formulations could be used as antipsychotic nasal drug delivery to overcome sulpiride low oral bioavailability (Ayoub et al. 2016). Optimized eugenol-NE prepared using Tween 80 and Labrasol as surfactant and cosurfactant, respectively showing hydrodynamic diameter 89.98±6.48nm, PDI of 0.238±0.021 and zeta potential of -10.05±0.11 mV were found to enhance the transdermal delivery of eugenol without causing skin irritation (erythema and edema) *in vivo* suggesting their potential to be used in wounds healing and anti-inflammatory treatments (Ahmad et al. 2018a). The NE containing cumin EO/oleic acid and Tween 20/ethanol (2:1) showed high phenolic encapsulation efficiency and remarkable cumulative phenols permeation through rat skin as well as high *in vitro* and *in vivo* antioxidant efficiency and provided high hepatoprotective potential and reserved rats' body weight after a period of seven days of a single transdermal application (Mostafa et al. 2015b).

Staphylococcus aureus treated with optimized NE containing eucalyptus oil as organic phase, water as continuous phase, and non ionic surfactant, Tween 80, as emulsifier prepared by 30 min sonication and showing the mean droplet diameter of 3.8 nm resulted in complete loss of viability within 15 min of interaction and the membrane of treated bacterial cells was damaged. This NE was not irritant and exhibited higher wound contraction rate in Wistar rats with respect to control and neomycin treated rats (Sugumar et al. 2014).

The optimized W/O NE of thiocolchicoside (TCC), an effective therapeutic agent against the orthopedic, traumatic and rheumatologic disorders, containing in ratio 1:1 linseed and sefsol (propylene glycol caprylate) as the oil phase, showed mean globule diameter of 117 nm, PDI of 0.285 and the steady-state flux (J_{ss}) and permeability coefficient (K_p) of 30.63±4.18 μg/cm^2/h and 15.21×10^{-3}±2.81 cm^2/h, respectively in *in vitro* permeation experiment using porcine skin suggesting that W/O NEs, which are compatible with the lipophilic sebum environment of the hair follicle, facilitate the transport of TCC, which might be predominantly transfollicular in nature (Kumar et al. 2016).

Curcumin (CUR) NE for transdermal application with mean droplet diameter, PDI and zeta potential of optimized NE 85.0±1.5 nm, 0.18±0.0 and -5.9±0.3 mV, respectively notably improved the permeation flux of CUR from the hydrophilic matrix gel Viscolam AT 100P (sodium polyacryloyldimethyl taurate, hydrogenated polydecene, polyoxyethylene), whereby NE formulation not only improved CUR permeability but also protected the drug from chemical degradation (Rachmawati et al. 2015). CUR-loaded NE (droplet size of 41.13±3.34 nm and zeta potential of -33.1±1.45 mV) that was incorporated into gel using carbopol-980 (1% w/v) and tested on Freund's complete adjuvant induced arthritic rat model after topical application of CUR-NE gel in Wistar rats showed substantial reversal of arthritic symptoms suggesting that the nanoformulation could exhibit therapeutic effects locally in inflammatory arthritic disorders with improved topical bioavailability (Naz and Ahmad 2015). Study of CUR distribution in neonate pig skin using CUR-loaded myristic acid microemulsions showed dermal CUR accumulation (326 μg/g skin) and transdermal CUR penetration (87 μg/cm^2/d). CUR encapsulated in ME inhibited bacterial growth of *Staphylococcus epidermidis* (EC_{50} of 0.86 μg/mL) and was found to be 12-fold more effective than CUR dissolved in dimethyl sulfoxide suggesting that such MEs could be used as alternative treatment for *S. epidermidis*-associated diseases and acne vulgaris (Liu et al. 2012).

NEs composed of propylenglycol, Transcutol®, water, Labrasol®, Plurol Oleique®, isostearyl isostearate, oleic acid, and D-limonene with incorporated imipramine or doxepin in the NE system (3% w/w) were tested for an analgesic and anti-allodynic activity at transdermal delivery of drugs and it was found that *in vivo* analgesic and anti-allodynic activity in rats was stronger for the doxepin loaded NE suggesting that such nanoformulation could be an alternative analgesic therapy with a potential clinical application (Sandig et al. 2013).

NEs consisting of mono ammonium glycyrrhizinate, Span 80, Brij 35, isopropyl alcohol, soyabean oil and distilled water were reported as appropriate vehicles for transdermal delivery of glycyrrhizin through human cadaver skin and while excipients of NEs acted as permeation enhancers themselves, the use of additional permeation enhancers was not necessary (Harwansh et al. 2011).

2.4.2 Nanoemulsions for cancer therapy

Surface modification of nanocarriers could contribute to their enhanced functions in imaging, targeting and delivery, increase drug bioavailability, reduce undesirable side effects, and minimize non-specific uptake, thus allowing specific cancer targeting to certain target (Yu and Zhang 2009). NEs in the translational research and their role in targeted cancer therapy were summarized by Ganta et al. (2014). The current status of NEs in the cancer therapeutics and commercial field on the basis of morphology, formulation, characteristics and characterization parameters was overviewed by Sahu et al. (2017). Sasikumar and Kamalasanan (2017) analyzed the possibilities of exploring NE platform for targeted drug delivery to prostate cancer. Recent advances in lipid nanocarriers, including NEs, applicable in the fight against cancer were summarized by Jampílek and Kráľová (2019b).

Zhao et al. (2018b) reported that woody oil-based emulsive nanosystems could efficiently deliver poorly soluble natural alkaloids resulting in increases in the sensitivity of lung cancer cells. O/W cinnamon oil NE (40.52 nm) and vitamin D encapsulated cinnamon oil NE (48.96 nm) showed anti-cancerous activity in human alveolar carcinoma cells, they induced DNA damage along with corresponding increase in micronucleus frequency, arrested the cell cycle progression in G_0/G_1 phase, showed increased expression of Bax, capase-3 and caspase-9 and decreased expression of BcL2 proteins along with considerable increase in apoptotic cell population and loss of mitochondrial membrane potential (Meghani et al. 2018). The antitumor potential of both O/W NE with encapsulated vitamin K_2 (VK_2) and NE incorporating VK_2 with a ligand conjugate sialic acid-cholesterol (showing enhanced affinity towards the membrane receptors overexpressed in tumors) anchored on the surface was evaluated in S180 murine sarcoma tumor cells. It was found that i.v. or intragastric administration of VK_2 NE to syngeneic mice with subcutaneously established S180 tumors resulted in considerable tumor growth suppression, higher effect being observed with surface-modified NE and both NEs were non-toxic (Shi et al. 2018).

Ahmad et al. (2018b) reported that the optimized silymarin NE with mean particle size of 21.24 nm reduced the cancer cell viability, increased intensity of reactive oxygen species (ROS) and chromatin condensation and could be considered as an efficient carrier for oral delivery of silymarin against human hepatocellular carcinoma without damaging normal cells. Methyl jasmonate loaded NE with mean droplet size of 75.06 nm and PDI 0.017 was found to be more effective in killing cancer cells, it induced a stronger sub-G_1 arrest than methyl jasmonate solution and showed a considerable absence of toxicity in human umbilical vein endothelial cells (Habibi et al. 2017). The EC_{50} values related to cytotoxic activity against A549 tumor cell line (human lung carcinoma) estimated with pure *Casearia sylvestris* Sw. extract and its NE were 4.0 μg/ mL and 1.0 μg/mL, respectively suggesting 4-fold higher efficiency of the nanoformulation (Pereira et al. 2017).

The cytotoxic effect of exopolysaccharides extracted from brown seaweed (*Sargassum longifolium*) encapsulated in orange oil NE with particle size 178 nm and zeta potential -43.9 mV estimated by MTT method in colon (HCT 116) cell lines was lower (70%) than that of seaweed polysaccharide encapsulated with nanostructured lipid carrier (Shofia et a;. 2018). Weekly i.v. administration of O/W NE encapsulating DHA-SBT-1214, a novel ω-3 fatty acid conjugated taxoid prodrug against prostate cancer stem cells, to NOD/SCID mice bearing subcutaneous PPT2 tumor xenografts resulted in strong suppression of tumor growth compared to Abraxane® and placebo NE and viable cells that survived from this *in vivo* treatment regimen were no longer able to induce floating spheroids and holoclones (Ahmad et al. (2017). Migotto et al. (2018) developed a cationic bioadhesive NE surface modified with CS and particle sizes of 46.3 nm for intraductal administration of C6 ceramide showing 4.5-fold lower EC_{50} value of C6 ceramide related to the reduction of MCF-7 cells viability and this NE prolonged drug localization for more than 120 h in the mammary tissue following intraductal administration compared to its solution. NEs prepared using tanshinone extract of *Salvia miltiorrhiza* with the mean particle size of 14.2 nm inhibited human lung carcinoma cell (A549) proliferation more effectively than the

extract alone, they penetrated into cytoplasm through endocytosis and caused up-regulation of p-JNK, p53 and p21 and down-regulation of CDK2, cyclin D1 and cyclin E1 expressions in a dose-dependent manner and caused cell cycle arrest at G_0/G_1 phase (Lee et al. 2016). NE formulation of *Nigella sativa* L. EO with droplet diameter 20–50 nm notably reduced the viability of MCF-7 breast cancer cells, whereby the treated cells included cell membrane blebbing, cytoplasmic vacuolation, marginalization of chromatin, and fragmentation of the nucleus suggesting induction of apoptosis in MCF-7 cells (Periasamy et al. 2016).

O/W NE coated with a thiol modified CS designed for co-delivery of piperine (weight ratio 100: 1) was fabricated and high degree of CS modification with particle sizes of 110 nm did not show any cytotoxic effect on normal fibroblasts and promoted death in colon cancer cells (Vecchione et al. 2016). Formulation of diallyl disulfide and α-linolenic acid prepared as protein NEs showing antioxidant and radical scavenging property and acting also as optimal H_2S slow-release donors exhibited considerable anti-proliferative effect on MCF-7 breast cancer cell lines and HuT 78 T-cell lymphoma cells, induced apoptosis and cell cycle arrest at the G_0/G_1 phase and improved the Lin^- $Sca1^+$ human cardiac progenitor cells proliferation suggesting that they could be used in selective cancer therapy and for promoting the muscle tissue repair (Ciocci et al. 2016).

Evaluation of anticancer activities of ginger EO (GEO) and frankincense EO (FEO) NEs prepared by a high-pressure homogenization technique with incorporated antineoplastic agent, mitomycin C (MMC) showed that NE-based EOs ameliorated the apoptotic effects of MMC on the cancer cells (IC_{50} values of GEO-MMC and FEO-MCC NEs estimated for HeLa cells were reduced by 44.12 and 29.42 folds, respectively, while those for MCF-7 cells were decreased by 29.29 and 55.3 folds when compared to MMC solution). FEO-MMC NE caused also the greatest change on the HeLa cellular morphology, while MCF-7 cells were most damaged and their nuclei were segmented when subjected into high GEO-MMC NE. Consequently, mixing of drug with GEO NE and FEO NE considerably improved its cytotoxicity on the MCF-7 and HeLa cells (Al-Otaibi et al. 2018). MMC formulated into NEs based on EOs of chamomile (ChEO) and garlic (GarEO) reduced the cell viabilities of HeLa cervical cancer cells by 42- and 20-fold compared to free MMC, whereby treatment with GarEO NE or GarEO-MMC NEs resulted in stronger alteration of the cell membrane of the HeLa cells than treatment with ChEO or ChEO-MMC NEs. Using staining with 4′,6-diamidino-2-phenylindole it was found that NEs of GarEO and GarEO-MMC have got attached to the cell membrane causing damage to the cell, while those of ChEO or ChEO-MMC passed the cell membrane and affected the nucleus directly (Alkhatib et al. 2018a).

In vitro cytotoxicity against MCF-7 and HeLa cells of an albumin anchored docetaxel (DTX) lipid NE was higher than that of the plain NE, and in *in vivo* experiment it caused 80.01±2.74% inhibition of solid tumours induced in C57BL/6 mice compared to 55.62±5.41% inhibition caused by administration of the plain NE, whereby also its tumour targeting activity was 3-fold higher than that of plain NE (Afzal et al. 2016b). Transferrin coupled DTX lipid NE (200–393 nm) prepared by homogenization and ultra-sonication process caused 84.66±4.29% tumor inhibition in tumor induced C57BL/6 mice and was found to have also 3.54-fold higher tumor targeting activity compared to the plain lipid NE (Afzal et al. 2016c).

Carvacrol NE showing a negative surface charge of -29.89 mV and 99.1 nm mean droplet size powerfully induced apoptosis in doxorubicin (DOX)-resistant A549 lung carcinoma cells (A549DR), displayed cell senescence leading to cell cycle arrest and inhibited the autophagy suggesting that it could be used as a potential candidate for lung cancer therapy (Khan et al. 2018).

Paclitaxel (PTX) NEs, in which α-tocopherol oil core of Tocosol™ was substituted with γ-tocotrienol, and D-α-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS) with PEGylated γ-tocotrienol showing droplet size <300 nm were tested against Bx-PC-3 and PANC-1 pancreatic tumor cells. Fastest release was observed with NEs loaded with free PTX, when γ-tocotrienol was used as the core and anticancer activity was improved also by substituting α-tocopherol with γ-tocotrienol and pronounced increase in activity was estimated when PTX lipid

conjugates were used (Abu-Fayyad et al. 2018). Entrapment of gemcitabine-γ-tocotrienol conjugates into NEs pronouncedly improved their anticancer activity against Bx-PC-3 and PNAC-1 pancreatic cancer cells when compared to the free drug. Moreover, it was found that gemcitabine-γ-tocotrienol conjugates were least affected by deamination deactivation reaction *in vitro* when compared with the free and conjugated gemcitabine in solution (Abu-Fayyad and Nazzal 2017). CUR/δ-T3 tocotrienol NEs with average particle size of 261 nm, PDI 0.27 and zeta potential of 35 mV significantly suppressed constitutive NF-κ B activation, and significantly induced apoptosis in breast and ovarian cancer cells, MCF-7 and OVCAR-8 (Steuber et al. 2016). Hyaluronic acid-complexed PTX NEs containing DL-α-tocopheryl acetate and soybean oil with a diameter of 85.2±7.55 nm and a zeta potential of -35.7±0.25 mV administered at a dose of 25 mg/kg to nude mice transplanted with CD44-overexpressing non–small cell lung carcinoma cells (NCI-H460) xenografts suppressed cancer cell growth more than the Taxol® and strongly inhibited tumor growth, which could be connected with the specific tumor-targeting affinity of HA for CD44-overexpressed cancer cells (Kim and Park 2017a). HA-coated NEs composed of DL-α-tocopheryl acetate, soybean oil, polysorbate 80, and ferric chloride incorporating PTX with particle diameter and zeta potential of 65±15 nm and -39.5±0.33 mV, respectively showed superb targeting of ovarian SK-OV-3 tumor cells overexpressing CD44 (Kim and Park 2017b).

The study of the antitumor activity and cardiotoxicity of the garlic oil (GarO) NE and GarO NE with incorporated DTX with particle sizes 63.19±1.85 nm and 110.±14.37 nm, respectively in Ehrlich ascites carcinoma (EAC)-bearing mice showed that the administration of GarO NE enhanced the lactate dehydrogenase activity in the ascetic fluid and ameliorated the heart enzymes, while treatment with DTX-Gar NE improved the mean survival time of the mice (27.7±11.63 days) that at treatment with aqueous DTX solution reached 23.1±1.52 days (Alkhatib et al. 2017a). It is important to note that incorporating the DTX into NEs based on orange oil also improved its antitumor efficacy and reduced its cardiotoxicity in female Swiss Albino mice bearing Ehrlich tumor in their ascetic fluid (Alkhatib et al. 2017b). Efficient accumulation of NEs incorporating fraxinellone (Frax), an anti-fibrotic drug, prepared by an ultrasonic emulsification method with a particle size approx. 145 nm in the tumor site after systemic administration was observed and NE was taken up by tumor-associated fibroblasts (TAFs) and tumor cells. Following i.v. administration of Frax NE a notable decrease in TAFs and stroma deposition was estimated and an increase of natural-killer cells, cytotoxic T cells as well as a decrease of regulatory B cells, and myeloid-derived suppressor cells in the tumor microenvironment suggested that this treatment remolded the tumor immune microenvironment as well. Enhanced tumor-specific T-cell infiltration, activated death receptors on the tumor cell surface and increased apoptotic tumor cell death was achieved using combination of a tumor-specific peptide vaccine with Frax NE suggesting that such approach could be an effective and safe strategy to remodel fibrotic tumor microenvironment resulting in enhanced immune response activation and thus, in a prolonged efficiency for advanced desmoplastic melanoma (Hou et al. 2018). Improved *in vivo* antitumor activity in female Swiss Albino mice inoculated with Ehrlich ascietes and reduced hepatotoxicity was observed also with sorafenib incorporating NE formulated with flaxseed oil with particle diameter and zeta potential of 77.46±8.28 nm and -3.4±1.2 mV, respectively (Alkhatib et al. 2017c). Similarly, incorporation of sorafenib into carrot seed oil NE improved the antitumor efficacy of drug and reduced its hematoxicity and hepatotoxicity (Alkhatib et al. 2018b).

Acid-sensitive lipidated DOX prodrug (C16-DOX) entrapped in lipid NE improved chemotherapeutic index and tumor-control efficacy in an *in vivo* murine 4T1 breast cancer model compared to free drug and caused considerable reduction in lung metastasis due to possibility using higher dose of DOX (Camara et al. 2017). Folate-functionalized soy lecithin lipid NEs of DOX and ytrium 90 (^{90}Y) were found to inhibit growth of folate receptor rich nasopharyngeal carcinoma (NPC) cells CNE1 *in vitro* and pronouncedly decrease tumor volume in NPC-induced nude mice compared to DOX + ^{90}Y-lipid NE, causing massive (89.9%) necrosis and hemorrhage of CNE1 cells but lower growth inhibition (21%) of folate deficient nasal epithelial cells (RPMI

2650) than DOX + ^{90}Y-lipid NE (43.65%) (Liu et al. 2017). DTX NE containing as biocomponents soybean oil and lecithin with droplet size, PDI and zeta potential 233.23±4.3 nm, 0.240±0.010 and -43.66±1.9 mV, respectively exhibited strong cytotoxic activity against MCF-7 cancer cells (IC_{50}: 13.55±0.21 µg/mL at 72 h) as well as 2.83-fold higher cell uptake than control, whereby at a dose of 20 mg/kg no toxicity or necrosis was observed with liver and kidney tissues of mice (Verma et al. 2016). DTX NEs surface-functionalized with folate with particle sizes <150 nm showed a 270-fold decrease in IC_{50} value in chemoresistant ovarian cancer cells SKOV3TR as compared to DTX alone, while in SKOV3 tumour-bearing mice these NEs delivered DTX by folate receptor mediated endocytosis resulting in cytotoxicity capable of overcoming ABC transporter mediated taxane resistance (Ganta et al. 2016). Folate-PEG-decorated DTX lipid NE was superior in tumor targeting by 4.81- and 2.08-fold over controls and in tumor regression as well providing better results as PEGylation, albumin and transferrin strategies (Afzal et al. 2016a).

Theranostic NEs incorporating PTX and contrast agents prepared using linear polyglycerol-poly(ε-caprolactone) diblock copolymers and ethiodized poppyseed oil, lipiodol, as a core oil exhibited superb anticancer activities against HeLa ovarian cancer cells as well as the ability to be used as a contrast agent (Le Kim 2017). NE with co-encapsulated PTX and baicalein (5,6,7-trihydroxyflavone) showed better antitumor efficacy in MCF-7/Tax cells exhibiting progressive resistance to PTX *in vitro* as well as much higher antitumor efficacy *in vivo* than other PTX formulations suggesting that this NE formulation could be used to overcome multidrug resistance via oxidative stress augmentation and P-glycoprotein inhibition (Meng et al. 2016).

Multifunctional smart CUR-loaded CS/perfluorohexane nanodroplets of 101.2 nm and 77.8% CUR entrapment designed for contrast-ultrasound imaging and on-demand drug delivery showed notably higher inhibition of 4T1 human breast cancer cells *in vitro* by ultrasound exposure, suggesting that they could have a great potential for image-guided cancer therapy (Baghbani et al. 2017). Ultrasound-responsive multifunctional smart alginate/perfluorohexane nanodroplets with the mean particle size of 55.1 nm designed for co-delivery of DOX and CUR and showing 92.3% entrapment efficiency of DOX exhibited enhanced cytotoxicity in adriamycin-resistant A2780 ovarian cancer cells compared to DOX nanodroplets due to synergistic effects of DOX and CUR and their combined application with ultrasound irradiation leads to strong tumor regression (Baghbani and Mortarzadeh 2017). MEs of CUR with docosahexaenoic acid (DHA)-rich oil showed strong cytotoxicity on human glioblastoma U-87MG cell line (IC_{50}: 3.755±0.24 ng/mL), which could be a attributed to the synergistic effect of CUR and DHA in the ME and following administration of this ME to Sprague-Dawley rats the CUR concentration at 24 h achieved 466-fold (for intranasal) and 421-fold (for intravenous) of the IC_{50} value estimated in the U-87MG cell line suggesting that designed ME could be used for therapy of brain cancer by both routes of administration (Shinde and Devarajan 2017).

Photodynamic therapy (PDT) is a clinically approved cancer therapy utilizing photochemical reaction between a light activable molecule or photosensitizer, light, and molecular oxygen resulting in formation of reactive oxygen species that directly damage cells and/or vasculature leading to tumor destruction and induce inflammatory and immune responses (van Straten et al. 2017). For both hydro-alcoholic extract from *Tectona grandis* L.f. leaves (TGE) alone as well as extract incorporated into O/W NE with particles sizes approx. 20 nm and tested against melanoma B16 F10 cells photodynamic effect was estimated due to increasing toxicity under illumination with red light, however NE formulation was much less toxic towards normal cells in the dark compared to free TGE, which exhibited notable dark toxicity towards both B16 F10 and murine fibroblast NIH3T3 cells (Furtado et al. 2017). Acai oil in NE, a novel photosensitizer for PDT, applied at PDT treatment of NIH/3T3 normal cells and B16F10 melanoma cell lines caused 85% cell death for melanoma cells, while maintaining high viability in normal cells and tumor volume reduction of 82% in tumor bearing C57BL/6 mice was observed following 5-fold treatment with PDT using acai oil in NE (Monge-Fuentes et al. 2017). Magneto low-density NE (MLDNE) that can carry maghemite NPs and Chlorin e6 (Phytochlorin) as an active photosensitizer drug was designed as a potential vehicle for combined hyperthermia and PDT to

treat cancer, because it is selectively taken up by MCF-7 cancer cell surfaces with receptor recognition based on the overexpression of low density lipoprotein receptor. MLDNE showing particle size <200 nm and high drug encapsulation efficiency was found to enhance tumor damage after minor heat dissipation and/or minimum visible light photosensitization doses by classical magnetic hyperthermia and PDT resulting in notable synergic action on MCF-7 cells reflected in reduced cell viability (Pellosi et al. 2018). de Matos et al. (2018) studied the effects of PDT on cellular viability using CUR NE as a photosensitizing drug in cervical carcinoma cell lines and found that NEs were internalized inside cells and were observed in the intracellular environment for up to 36 hours after incubation with cell lines, whereby after the PDT high phototoxic effect of CUR NE (<5% of viable cells after irradiation) was estimated suggesting that CUR NEs have potential as an alternative treatment to cervical lesions using an endoscopic diode fiber laser setup for *in situ* activation or cavity activation using a diffuse fiber delivery system.

2.4.3 Nanoemulsions for pulmonary drug delivery

Optimized quercetin loaded O/W NE prepared using palm oil ester/ricinoleic acid as oil phase (droplet size of 131.4 nm, PDI 0.257, zeta potential 51.1 mV) showing good stability against phase separation and storage at 4°C for 3 months induced cytotoxicity towards A549 lung cancer cells without affecting the normal cells suggesting that NE could be used as a potential carrier system for pulmonary delivery of molecules with low water solubility (Arbain et al. 2018).
Minz and Pandey (2018) designed recombinant hepatitis B surface antigen loaded solid fat NEs as carrier system and monophosphoryl lipid A as an adjuvant-carrier system and evaluated it as multiadjuvanted vaccine system for deep pulmonary vaccination. The observed humoral (sIgA and IgG) and cellular (IL-2 and IF-γ) immune responses considerably exceeded those estimated with naive antigen (recombinant surface antigen without any excipient) solution.
Nasr et al. (2014) used commercially available lipid NE, the Intralipid® or Clinoleic®, to prepare amphotericin B lipid NE aerosols for targeting peripheral respiratory airways via nebulization.
Tea tree oil NEs prepared using Cremophor EL (average size of 12.5 nm) exhibited excellent antimicrobial activities on *Escherichia coli*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *S. aureus* and *Candida albicans* and after inhalation to the lung showed higher anti-fungal effect than fluconazole on the fungal pneumonia rat models, causing reduced lung injury, highly microbial clearance, blocking of leukocyte recruitment, and decrease of pro-inflammatory mediators. Such inhalable formulation could be used in local therapies of fungal and bacterial pneumonia with no obvious adverse events (Li et al. 2016a).
Shah et al. (2017) tested rifampicin-oleic acid first-generation NE and its respective CS- and CS-folate conjugate-decorated second and third-generation NEs showing mean droplet sizes of 40−60 nm related to aerosolization, pulmonary inhalation, intracellular trafficking potential in macrophages and pharmacokinetics profiles. Chitosan oligosaccharide lactate was employed as mucoadhesive, bioadhesive and targeting moiety for macrophages, while folic acid was used as targeting ligand of macrophage. It was found that tested NEs exhibited >95% aerosol output and inhalation efficiency >75% and the size and surface tension of NEs affected the aerosol output, aerosolized and inhaled fine particle fractions in an inverse relationship. Higher cell internalization potential, reduced plasma drug concentration, and higher lung drug content showed third-generation NEs. NE containing highly-refined soybean oil together with cetyl pyridinium chloride, Tween 80 and ethanol in water produced by high-speed emulsification showing droplets with mean diameter of 450 nm and safe mucosal adjuvants, when delivered intranasally along with *Mycobacterium tuberculosis* specific immunodominant antigens, induced potent mucosal IL-17 T-cell responses and conferred protection upon *M. tuberculosis* challenge in mice. Moreover, when such NE tuberculosis vaccine is delivered along with *Mycobacterium bovis* bacillus Calmette-Guerin licensed vaccine, decreased disease severity could be observed (Ahmed et al. 2017).

2.4.4 Nanoemulsions for ocular drug delivery

Nanotechnology-based systems for treating and managing various ocular diseases include more accessible formulations for deeper segments of the eyes, which enable the availability of drugs at required site in a required amount without inversely affecting the eye tissues (Lalu et al. 2017). Findings related to topical application of lipid-based systems (MEs, NEs, liposomes and solid lipid NPs), polymeric systems (hydrogels, contact lenses, polymeric NPs and dendrimers) and used physical methods (iontophoresis and sonophoresis) was reviewed by Souza et al. (2014). The use of nanocarriers, including NEs for gene therapy of retinal diseases, was overviewed by Al-Halafi (2014).

Coumarin-rich extract from *Pterocaulon balansae* incorporated into NEs composed of medium chain triglycerides (MCT) and egg-lecithin with droplet sizes >300 nm caused a 95% reduction of trophozoite viability after 24 h of incubation with a NE containing 1.25 mg/mL of coumarins, whereby the effect was comparable with that of chlorhexidine suggesting potential of such NEs to be used for the local treatment of ocular keratitis caused by *Acanthamoeba* (Panatieri et al. 2017).

Castor oil and mineral oil NEs with mean particle size of 234 nm, PDI >0.16, zeta potential of -8.562±3.49 mV, slightly acid pH and viscosity of about 1.2 cP, which were instilled on the surface of a commercial contact lens, were found to be situated inside and on the surface of the lenses and their transparency remained near 100% suggesting their suitability for ocular application, because the contact lens remained transparent and ion-permeable after association with this formulation (Katzer et al. 2014).

The introduction of a positive charged mucoadhesive polymer, CS, into NEs designed for ocular administration of timolol containing the drug as maleate or as ion-pair with bis(2-ethylhexyl) sulfosuccinate increased drug permeation probably due to the interaction of CS with corneal epithelial cells (Gallarate et al. 2013).

A combination of NE with 2% hydroxyethyl β-cyclodextrin resulted in 9.2-fold higher lutein accumulation (119±6 μg/g/h) compared to lutein suspension alone and the scleral accumulation of lutein increased by increasing the cyclodextrin content, whereby the nanoformulation showed low cytotoxicity in retinal cells (Liu et al. 2015a). Lutein-loaded NE consisting of isopropyl myristate, triacetin, Tween 80, and ethyl alcohol with particle sizes approx. 10–12 nm showed sustained and pronouncedly increased lutein release. Such NE could be considered as a potential alternative delivery system for lutein, an effective drug used in therapy of macular degeneration (Lim et al. 2016).

Dexamethasone acetate (DEX) and polymyxin B sulfate were formulated as a cationic NE, in which soy phosphatidylcholine represented 30% of the lipid phase containing DEX, while polymyxin B sulfate was dissolved in the water phase and this NE could be considered as a viable alternative to the commercial ophthalmic suspensions designed for the treatment of ophthalmic infections (Li et al. 2016b). Triamcinolone acetonide-loaded NE consisting of MCT oil, soybean lecithin and Poloxamer 188 released the drug in a fast rate and could provide an adequate drug release rate on the eye surface to be used in topical ophthalmic administration (Silva and Lemos-Senna 2016).

Alternative controlled-release ocular terbinafine hydrochloride-loaded NE *in situ* gels prepared by NE dispersion in gellan gum solution (0.2%, w/w) were transparent, pseudoplastic, mucoadhesive, showed more retarded zero-order drug release rates and increased bioavailability (Tayel et al. 2013).

Acetazolamide loaded NEs fabricated using peanut oil, Tween 80 and/or cremophor EL as surfactant and transcutol P or propylene glycol as cosurfactant were incorporated into ion induced *in situ* gelling systems composed of gellan gum alone and in combination with xanthan gum, hydroxypropyl methylcellulose (HPMC) or carbopol. The gels showed a considerably sustained drug release in comparison to the NEs, whereby gellan/xanthan and gellan/HPMC exhibited improved therapeutic efficacy and more prolonged intraocular pressure lowering effect relative to that of commercial eye drops and oral tablet (Morsi et al. 2017).

Cyclosporine A (Cy-A) NEs containing oleic acid, Tween 20 and Transcutol P and coated with CS were evaluated as non-irritant and non-toxic, being well tolerated by rabbit eye much more sensitive than human. In corneal penetration studies for low molecular weight CS coatings 59.2 and 57.5% of drug penetration was estimated, while for medium high molecular weight CS coatings it was 55.5% and 52.3%, respectively (Shen et al. 2018). Optimized Cy-A loaded polymeric mucoadhesive NE with higher Cy-A payload, in which the concentration of CS was adjusted according to the blinking force of eyelids, was able to maintain the therapeutic concentrations (≥50−300 ng/g) of drug in the rabbit cornea and conjunctiva over the period of 24 h (Akhter et al. 2016).
Celecoxib NE containing 5% oleic acid-Transcutol P (10:1) in oil phase with droplet sizes ranging from 6.96 to 26.65 nm and pH 6.5−6.9, respectively showed 82.6% of the drug released in the 24 h of the experiment. NE containing 85% of surfactant (Tween 80, Span 20) and cosurfactant (propylene glycol) in a ratio 2:1 showed that 15.73% drug permeated through rabbit cornea and the flux (J_{ss}) of Celecoxib from this NE (0.65 mg cm^{-2}/h) was 22-fold higher than this of control (Moghimipour et al. 2017).

2.5 Nanoemulsions applicable in food industry

There are various nanocomposites suitable for the protection of different foodstuffs, smart active or responsive packaging materials, edible coatings, as well as diverse nanosensors applicable for monitoring of food quality, safety, and integrity and the application of nanocomposites in food packaging systems could diminish the harshness of food processing and the amount of additives and chemical preservatives in food industries (e.g., Jampílek and Kráľová 2018b). Nanoemulsion technology is particularly appropriate for the preparation of encapsulating systems for functional compounds, because it prevents their degradation and improves their bioavailability. An overview of food-grade NEs, their recent applications in the food systems and patent review of emulsions was presented by Yalcinoz and Ercelebi (2018). Promising advantages reached with the use of NEs as delivery systems of flavoring and preservative agents in the food industry were summarized by Salvia-Trujillo et al. (2015). Adjonu et al. (2014) overviewed emulsifiers/surfactant (ionic, non-ionic, phospholipid, polysaccharide, and protein) used in NEs designed for food applications as well as suitability of proteins and protein hydrolysates as nanoemulsifiers and analyzed the potential of whey protein derived peptides as both emulsifiers and bioactive compounds in NE delivery systems. The influence of particle characteristics such as size and interfacial properties on potential biological fate (digestion and absorption) of ingested NEs was described by McClements and Xiao (2012). The influence of droplet characteristics on the physicochemical and sensory properties of beverage emulsions, with special focus on their influence on product stability as well as developments in the soft drinks area, including fortification with vitamins, reduced calorie beverages, and "all-natural" products were overviewed by Piorkowski and, McClements (2014). Although to the potential advantages of food-grade NEs over conventional emulsions for applications in the food industry belong higher stability to particle aggregation and gravitational separation, higher optical transparency and increased bioavailability of encapsulated components, potential risks associated with consumption of lipid nanoparticles that are able to alter the fate of bioactive components within the gastrointestinal tract and possible toxicity of surfactants and organic solvents could not be marginalized (McClements 2013).

2.5.1 Nanoemulsions formulated with natural emulsifiers, biosurfactants and biopolymers

Mungure et al. (2018) overviewed the potential application of pectin, an anionic polysaccharide, for the stabilization of NE systems. Synthesis and applications of pectin-based nanomaterials that combine the advantages of both pectin and the nanoscale particles was overviewed by Zhao and Zhou (2016). Bai et al. (2016) compared the effectiveness of a number natural emulsifiers (whey

protein, gum arabic, *Quillaja* saponin and soy lecithin) at fabricating corn O/W NEs using dual-channel microfluidization and found that whey protein isolate and *Quillaja* saponin more effectively formed NEs with fine droplets than gum arabic and soy lecithin (lower amount of emulsifier needed, fabrication of smaller droplets), which could be connected with faster emulsifier adsorption and a greater reduction in interfacial tension resulting in more effective droplet disruption within the homogenizer for saponins and whey proteins. McClements and Gumus (2016) analyzed the possibility of the replacement of synthetic surfactants with natural emulsifiers, such as amphiphilic proteins, polysaccharides, biosurfactants, phospholipids, and bioparticles, discussed the physicochemical basis of emulsion formation and stabilization by natural emulsifiers and compared the benefits and limitations of different natural emulsifiers.

Konjac glucomannan, a renewable natural polysaccharide occurring in the tuber *Amorphophallus konjac* K. Koch, composed of β-1,4-linked D-mannose and D-glucose in either a 1.6:1 or 1.4:1 molar ratio, exhibit good swelling, gelling, or emulsifying properties. Its derivative, konjac glucomannan octenyl succinate (KGOS), was found to be a good potential emulsifier and stabilizer for encapsulation of lipophilic bioactive compounds such as β-carotene. Emulsification yield of the KGOSC nanoemulsion containing 0.03% β-carotene, 0.3% KGOS and 10% MCT exceeded 95% and after 30 days of storage, the particle size and PDI of the KGOSC NE did not reach 5 nm and 0.5, respectively, whereby the sensitivity of KGOSC NEs to storage conditions decreased in following order: temperature > oxygen > light (Li et al. 2018).

W/O NEs of Sacha Inchi oil (SIO), containing a very high content of the ω-3 fatty acid, α-linolenic acid (approx. 50%) and tocopherols (176–226 mg/100 g) prepared using olive leaf phenolics (OLP) showed droplet size 2.15±0.13 nm and were stable without phase separation during 30-day storage, whereby the release of OLP controlled the oxidative progress of SIO by prolonging the induction time, preventing the production of primary and secondary oxidative products and also the deterioration of polyunsaturated fatty acids and tocopherols (Liu et al. 2018). Among O/W NEs prepared with 10% avocado oil using natural (lecithin) and synthetic (Tween 80) emulsifiers at different concentrations (2.5–10%) with zeta potential ranging from -26 to -59 mV and lipid droplets of 103–249 nm, Tween 80 was found to be more effective than lecithin (Arancibia et al. 2017). Multilayer emulsions produced by a high-pressure homogenization method using an electrostatic layer-by-layer deposition process of lecithin-CS membranes encapsulating linseed oil and α-lipoic acid simultaneously were found to be an effective delivery system to incorporate them into functional foods and beverages. CS encapsulation inhibited the degradation of α-lipoic acid and improved the oxidation stability of linseed oil in multilayer emulsions that showed good centrifugal, dilution and storage stabilities (Huang et al. 2018).

Using MCT oil the rhamnolipids biosurfactants can effectively form small droplets (d_{32} <0.15 μm) at low surfactant-to-oil ratios (<1:10). Rhamnolipid-coated droplets were found to be stable to aggregation at pH values 5–9, salt concentrations <100 mM NaCl and 20–90 °C. Droplet aggregation at pH 2–4 and high ionic strength 200–500 mM NaCl could be connected with a reduction in electrostatic repulsion at low pH and high salt levels. Rhamnolipids could be considered as effective natural surfactants suitable to replace synthetic surfactants in certain commercial applications (Bai and McClements 2016).

Quillaja saponin (Q-Naturale®), a natural food-grade surfactant isolated from the bark of the *Quillaja saponaria* Molina tree, containing saponin-based amphiphilic molecules, was reported to be able to replace synthetic surfactants in food and beverage products (Yang et al. 2013). A promising NE delivery system for oregano as an essential oil model with long-term stability using a sugar-based biosurfactant (*Quillaja* saponin) produced by microfluidization was found to be suitable to be used in antimicrobial as well as flavoring and potential antioxidant applications in food and beverages or in pharmaceutical and cosmetic products (Doost et al. 2018).

The study of high pressure homogenized whey protein emulsions prepared by mixing whey protein concentrate (10%), soybean oil (0 or 5%) and soy lecithin (0 or 5%) showed that increasing homogenization pressures significantly decreased particle sizes of all samples but

increased electrical conductivity of samples. After 25 MPa treatment emulsions with lecithin had smaller particle sizes than those made without lecithin, but at 50 MPa further reduction of particle sizes in the presence of lecithin was not observed (Yan et al. 2017). Yerramilli et al. (2017) studied partially replacement of sodium caseinate (SCas) in the formation and long-term stabilization of 5 wt% O/W NEs prepared using a high-pressure homogenization by pea protein isolate (PPI) and found that NEs stabilized by 1:1 mixture of SCas and PPI did not display any creaming or aggregation and remained stable for more than 6 months (droplets <200 nm), which could be connected with the interaction of pea proteins disrupted by high-pressure homogenization with SCas in the continuous phase of the NEs. Consequently, the plant proteins have potential to be applicable in the long-term stabilization of NEs in the food and beverage industry. O/W NEs stabilized by high-pressure homogenized lentil proteins isolate (LPI) showed pronouncedly higher *in vitro* lipid digestibility than unmodified LPI NEs, which could be connected with the higher interfacial area of smaller droplets and weaker interfacial moduli of modified LPI-stabilized interfaces compared to those with unmodified LPI. It could be noted that high-pressure homogenization notably decreased LPI particle size distribution, surface hydrophobicity and the interfacial storage moduli relative to the unmodified LPI (Primozic et al. 2018).
As an attractive biosurfactant suitable for preparation of NE formulations applicable in food and beverage products saponin extracted of Brazilian ginseng roots was reported (Rosa et al. 2016).

2.5.2 Nanoemulsions of essential oils and their constituents

Excellent antimicrobial efficacy of plant EOs predestines them to be used as an alternative of health hazardous synthetic preservatives in food products and encapsulation of EOs in NEs, MEs, solid-lipid NPs and liposomes improve their shelf-life already at low doses (Prakash et al. 2018a). Donsi and Ferrari (2016) in a review paper focused their attention on EO NEs as antimicrobial agents in food, critically analyzed the reported antimicrobial activity data, both *in vitro* and in products and discussed the regulatory issues associated with their use in food systems. An overview related to the different systems for the encapsulation of bioactive oils and the currently applied elaboration methods was presented by Rodriguez et al. (2016).
Although EOs in the food industry are mainly used as flavoring agents, O/W NE of betel (*Piper betle* L.) leaf EO showed antimicrobial activity against five strains of Gram-positive and Gram-negative bacteria with MIC of 0.5–1.25 μL/mL and MBC of 1–2.5 μL/mL suggesting that it can serve as natural antimicrobial agent for food system (Roy and Guha 2018). Mexican oregano (*Lippia graveolens* Kunth) EO containing thymol and γ-terpinene, which was incorporated into active coatings and spread on fresh pork meat as free, nanoemulsified, and microencapsulated EO at a dose of 2.85 mg EO/cm^2 caused growth inhibition of *Lactobacillus plantarum* (5 log population reduction) and *Pseudomonas fragi* (4 log reduction), while ≤1.5 log population reduction was observed for *Brochothrix thermosphacta* and *Salmonella Infantis*, whereby meat microbiota was most efficiently controlled by microencapsulated EO resulting in delayed lipid and oxymyoglobin oxidation of fresh pork meat (Hernandez-Hernandez et al. 2017). Anise oil NE more effectively reduced the population of *E. coli* O157:H7 and *Listeria monocytogenes* (count by 2.51 and 1.64 log cfu/mL, respectively) than bulk anise oil (by 1.48 and 0.47 log cfu/mL) after 6 h of contact time (Topuz et al. 2016). The EO-based NEs could improve the microbial quality of minimally processed fruits and vegetables (Prakash et al. 2018b). Basil oil (*Ocimum basilicum*) NE fabricated by ultrasonic emulsification with droplet diameter 29.3 nm showed antibacterial activity against *E. coli* causing alteration in permeability and surface features of bacterial cell membrane (Ghosh et al. 2013). Long-term stability over 21 days of storage was estimated with *Zataria multiflora* Boiss EO NE (droplet size of 200 nm and PDI 0.2) fabricated by emulsion phase inversion that showed MIC values of 2500 and 5000 μg/mL against *L. monocytogenes* and *Salmonella typhimurium*, respectively and this NE was more effective in inhibiting the growth of bacteria in milk than in culture media (Shahabi et al. 2017).

Optimized clove oil NEs prepared using SCas (5%) and pectin (0.1%) as coating material by high speed homogenization with spherical NPs of 172.1±4.39 nm, zeta potential of -37±1.93 mV and EE of 88% showing stability at all food processing conditions except pH 3.0–5.0 could be recommended as delivery system for antimicrobial bioactive substances in food preservation (Sharma et al. 2017). Optimized ultrasound-mediated nettle oil (1.25 wt%) NEs stabilized by purified jujube polysaccharide with 86.75 nm droplet size inactivated the Gram-positive bacterium more effectively than the Gram-negative one (Gharibzahedi 2017). Stable NEs prepared by mixing eugenol with SCas using shear homogenization observed up to 38.5 mg/mL eugenol showed droplet diameters <125 nm at pH 5–9 after ambient storage for up to 30 days and more effective inhibition of *E. coli* O157:H7 than free eugenol during incubation at 37 °C for 48 h. A greater reduction of intracellular ATP and a greater increase of extracellular ATP was observed in bacteria treated with encapsulated eugenol (20 min interaction at 21 °C) compared to free eugenol suggesting enhanced permeation of eugenol due to its nanoencapsulation, although the possible membrane adaptation could not be excluded (Zhang et al. 2018). Salvia-Trujillo et al. (2014) reported that lemongrass oil–alginate NEs prepared by microfluidization exhibited enhanced antimicrobial activity against *E. coli*, while ultrasound processing of NEs led to loss of their bactericidal action.

Thyme O/W NEs (pH 3.5) were found to be highly unstable to droplet growth and phase separation, which could be connected with Ostwald ripening due to the relatively high water solubility of thyme oil. Inhibition of Ostwald ripening could be achieved by mixing thyme oil with a water-insoluble ripening inhibitor (≥60 wt% corn oil or ≥50 wt% MCT in the lipid phase) before homogenization, yielding NEs with good physical stability. However, ripening inhibitor type and concentration had a notable impact on the antimicrobial activity of EO and increasing the ripening inhibitor levels in the lipid phase resulted in the reduction of the antimicrobial efficacy of NEs (Chang et al. 2012).

Comparison of the *in vivo* oral bioavailability study of conventional emulsion (droplet diameter 1.285 μm) and NEs of vitamin E prepared using sunflower oil and saponin (droplet diameter 0.277 nm) showed that the *in vivo* oral bioavailability of vitamin E in male Wistar rats at NE application reached a 3-fold higher AUC compared to the conventional emulsion (Parthasarathi et al. 2016). Bovi et al. (2017) reported that NEs of Buriti (*Mauritia flexuosa* L.) oil, one of the richest vegetal sources of carotenoids, could be successfully incorporated in isotonic sports drink and replace the artificial coloring by natural dyes.

In O/W NEs stabilized by soy lecithin and encapsulating carvacrol the zwitterionic lecithin molecules adsorbed to the O/W interface for 24 h formed a notably viscoelastic layer, at pH 7 the NEs were highly stable, yielding monodispersed droplet size distributions and high resistance to increases in droplet size over 30 days, although the initial size of oil droplets slightly depended on pH (smaller droplets at pH 7 and larger droplets at pH 3) (Nash and Erk 2017).

Eugenol NE prepared by using ultrasonication as emulsification techniques, CS NPs as carrier, and Tween 20 surfactant as emulsifier, with regularly spherical shape and sizes ranging from 80 to 100 nm were characterized with great storage and thermal stability and exhibited superb antioxidant capacity and antimicrobial activity suggesting their great potential to be used in food formulations for extending the shelf life (Shao et al. 2018).

O/W chia seed oil NE systems prepared by spontaneous emulsification and microfluidization and stabilized with Tween 80 and Span 80, as well as SCas- and sucrose monopalmitate-stabilized NEs fabricated by microfluidization were characterized by storage stability at 4 °C during 2 weeks. The NEs prepared with sucrose monopalmitate showed best transparency with droplet diameter ca. 47 nm (Teng et al. 2018). Blended cloves/cinnamon EO NEs fabricated using Tween 80 surfactant and ethanol (cosurfactant) with oil to the mixed surfactant/cosurfactant ratio of 1:9 showed higher antimicrobial activity against *E. coli*, *B. subtilis*, *S. typhimurium*, and *S. aureus*, even at far lower concentrations than free EOs and this NE could be applied as a natural antimicrobial agent in food industry (Zhang et al. 2017).

Digested *Hibiscus cannabinus* L. seed O/W NEs stabilized by SCas, Tween 20 and β-cyclodextrin complexes produced using high pressure homogenization showed good lipid

digestion (85.25%), good bioaccessibility of antioxidants (tocopherols and total phenolic contents) and lower degradation rate of phytosterols compared to digested bulk oil suggesting potential use of such formulation in food and nutraceutical preparations (Cheong et al. 2016a). Addition of β-cyclodextrin to primary emulsion containing SCas and Tween 20 was found to improve the physical stability of kenaf (*Hibiscus cannabinus* L.) seed O/W NEs (Cheong and Nyam 2016).

Negatively charged NEs of black cumin EO fabricated using different ratios of EO with canola and flax seed oils (ripening inhibitors) that were stabilized with octenyl succinic anhydride (OSA) modified waxy maize starch (mean droplet diameter >200 nm and zeta potential above -30 mV) showed prolonged bactericidal activities against *Bacillus cereus* and *L. monocytogenes* than the pure black cumin EO, which could be explained with its better stability, controlled release and self-assembly with the cell membrane of Gram-positive bacteria resulting finally in destruction of cellular constituents (Sharif et al. 2017a).

Alexandre et al. (2016) reported about activated films with improved physical properties prepared by incorporation of montmorillonite and nanoemulsioned ginger EO into gelatin-based films with notably better elongation at break, puncture force and puncture deformation and showing antioxidant activity, which could be used in food packaging applications.

2.5.3 Vitamin nanoemulsions

The use of natural surfactants, *Quillaja* saponin and lecithin, on the formation and stabilization of NE-based vitamin E delivery systems was described by Ozturk et al. (2014). At simulated small intestine conditions, the rate of lipid digestion and tocotrienol bioaccessibility in bulk oil and within O/W conventional emulsions (>10 μm) and NEs (<350 nm) fabricated using MCT as an oil phase (5 to 40% wt) and *Quillaja* saponins as a natural surfactant decreased as follows: NEs > emulsions > bulk oil (Xu et al. 2018). The increase of the bioavailability of α-tocopherol as a food supplement could be secured through edible (coconut) oil NE showing a 9.5 mg/mL of encapsulation capacity and almost 100% release of the loaded active ingredient within 24 h, whereby the contribution of kinetic-controlled release was found approx. 70% and that of diffusion-controlled release was found approx. 30%. Beside of good stability of NE a reasonable cell viability (biocompatibility) with apposite antimicrobial activity was estimated suggesting potential application of such edible oil NE in food, beverages, and health care industries (Saxena et al. 2018). The α-tocopherol based O/W NE fabricated using sodium stearoyl lactate and Tween 80 surfactants by high energy ultrasonication method with encapsulated benzylisothiocyanate acted as better antioxidant compared to pure and CUR encapsulated NE; the prepared emulsions exhibited good stability up to 90 days in salt solution (50–200 mM) and different pH conditions and the degradation of CUR by UV light was successfully controlled by trapping in NE (Kaur et al. 2017).

The impact of antioxidants on the thermal stability of β-carotene encapsulated in diluted O/W) emulsions prepared using gum arabic decreased as follows: α-tocopherol > tertiary butyl hydroquinone > ascorbyl palmitate, the most effective antioxidant being α-tocopherol at the concentration of 0.10 wt% under light exposure (Liu et al. 2015b). Digested *Ulva fasciata* polysaccharide-stabilized emulsions encapsulating β-carotene (mean particle size of 0.82 μm) showed higher lipid digestion rate and increased β-carotene bioaccessibility than gum arabic- or beet pectin-stabilized emulsions suggesting that they could be a promising delivery system for β-carotene in functional food and beverage system. Moreover, the stability of β-carotene in the emulsion could be considerably increased by addition of α-tocopherol (Shao et al. 2017). NEs, in which fat soluble vitamins β-carotene and α-tocopherol were co-encapsulated using flax seed oil and octenyl succinic anhydride modified starch as emulsifier with incorporated eugenol showed overall higher retention of β-carotene (ca. 42%) and α-tocopherol (ca. 90%) after 4 weeks of storage at 40 °C as compared to NEs, in which Tween 80 was used as emulsifier, which could be

connected with the fact that the modified starch emulsifier can form a thicker protective layer around oil droplets (Sharif et al. 2017b).
Increased bioavailability of vitamin D encapsulated in O/W NE prepared by ultrasonication technique showing a droplet size 300–450 nm and shelf life >90 days in simulated gastrointestinal tract was reported by Walia et al. (2017). The ergocalciferol *in vitro* bioaccessibilities in O/W NEs prepared using emulsifiers with different stabilizing mechanisms were comparable for decaglycerol monooleate (62%; steric mechanism), modified lecithin (64%; electrostatic mechanism) or their combination (65%) but they were significantly higher than that estimated for SCas emulsifier (12%; electrosteric) and also the free fatty acids release rate in the small intestinal phase was the lowest for SCas (Shu et al. 2018).
Folic acid nanoencapsulated by double emulsions having an internal NE composed of W/O system with folic acid present in the water phase and reemulsified within an aqueous phase of pectin–whey protein concentrate complexes showed EE about 88.3%, whereby EE was predominantly affected by the dispersed phase content of double NE and surfactant had the minimum influence (Assadpour et al. 2016).

2.5.4 Nanoemulsions encapsulating fatty acids

Uluata et al. (2015) studied physical stability, autoxidation, and photosensitized oxidation of ω-3 oils in NEs prepared with natural (lecithin and *Quillaja* saponin) and synthetic (Tween 80 and sodium dodecyl sulfate) surfactants and found that lipid hydroperoxide decreased in the order Tween 80 > SDS > lecithin > *Quillaja* saponin, whereby *Quillaja* saponin consistently produced the most oxidatively stable emulsions, which could be due to its high free radical scavenging capacity.
NEs encapsulating fish oil prepared using MCT, lemon oil and thyme oil as carrier oils containing 75% fish oil and 25% carrier oil were physically stable for 42 days at 20 °C, whereby the rate of lipid oxidation in NEs decreased in the following order: MCT >> lemon oil > thyme oil, which could be connected with the presence of high levels of natural antioxidants (phenolics) within both essential oils (Walker et al. 2017). The oxidative stability of fish oil encapsulated in multiple NE with particle sizes 190–210 nm prepared using whey protein concentrate was enhanced, whereby key factors affecting the droplet size of NE and oxidative stability of fish oil were found to be whey protein concentrate concentration level and used antioxidant type (vitamin C and E) (Hwang et al. 2017).
Esquerdo et al. (2018) designed food-grade NEs containing unsaturated fatty acids (UFA) concentrates from carp oil, using CS and gelatin as wall materials, in which these biopolymers provided high stability to the formulations and also behaved as good wall materials, whereby at 90:10 of CS:gelatin ratio the NE was in the acceptable range of the legislation after 7 days of storage, suggesting the increase of the physical and oxidative stability of UFA and such NEs could facilitate the addition of these lipophilic active ingredients in aqueous-based foods or beverages. Application of NE in combination with vacuum packing was found to maintain the polyunsaturated fatty acids content of sea bass (*Dicentrarchus labrax*) fillets stored at 22 °C, since NE s with hazelnut, canola, and soybean oils can be used as a preservative for fish and such NEs together with vacuum packing could prevent the lipid oxidation (Ozogul et al. 2017).

2.5.5 Nanoemulsions encapsulating bioactive compounds

Gelatin based-films incorporated with rutin-loaded O/W NE displayed higher tensile strength and higher elongation at break than the gelatin control film, showed high antioxidant activities, rutin release being mainly governed by Fickian diffusion with simultaneous interfering swelling and disintegration phenomena and they could be considered as potential active packaging systems to enhance shelf life of food products (Dammak et al. 2017).
Quercetin loaded NEs fabricated using high pressure homogenization method with mean droplet size of 152±6nm, zeta potential of -50±2 mV and entrapment efficiency of 93.50±0.35%

exhibited comparable antioxidant activity to free quercetin and also the bioaccessibility of quercetin in simulated small intestinal conditions was found to be improved by nanoencapsulation (Ni et al. 2017). Optimized green tea catechins NEs prepared by high pressure homogenization with droplet diameter of 280±1 nm and 83.16±1.12% EE subjected to different environmental stress (pH, temperature and salt concentration) were stable for 8 weeks and showed slow and sustained release of polyphenols from lipid matrix in mimicked gastric conditions (Gadkari et al. 2017).

Milk fortified with CUR NEs prepared using high pressure homogenization exhibited pronouncedly lower lipid oxidation than unfortified (control) milk and milk containing CUR-free NEs suggesting that such CUR NE could be utilized in beverage industry (Joung et al. 2016). Active films based on gelatin-SCas blend containing active compounds (α-tocopherol, garlic essential oil and cinnamaldehyde) nanoemulsified in water showed good antioxidant activity suggesting their potential to be used as active packaging for shelf life extension of foodstuffs (Cordoba and Sobral 2017). Physically stable NE enriched with the carotenoid astaxanthin (droplet diameter of 230 nm; zeta potential of -40 mV) prepared using caseinate as emulsifier were stable in the temperature range 5–70 °C) and a wide range of pH (except at pH 4 and 5) and ionic strength could be used in functional foods and beverages (Liu et al. 2016).

Lecithin-containing emulsions of capsaicin (mean particle size 582.63 nm) showed high antimicrobial activity against *S. aureus* with 4.60 log reduction, while with the capsaicin encapsulated NE prepared using Tween 80 as surfactant (mean particle size 68.30 nm) a 3.86 log reduction against *E. coli* was estimated (Akbas et al. 2017).

Quercetin trapped saponin stabilized NEs with mean particle size of 52±10 nm exhibited higher stability on exposure to UV light as compared to water/ethanol system showing the degradation rate 9±1% (at pH 7) and 11±1% (at pH 8.0) as compared to 42±2% in water/ethanol system (Kaur et al. 2016).

The thermal resistance of *L. monocytogenes* was reduced from 2- to 5-fold, when 0.5 mM D-limonene was added directly to the heating medium. However, the presence of the same D-limonene concentration in the heating medium in the form of NE reduced heat resistance of *L. monocytogenes* by one hundred times compared to 2–5 reduction at application of free D-limonene suggesting that the addition of nanoemulsified antimicrobials can pronouncedly reduce the intensity of the thermal treatments currently applied in the food processing industry (Mate et al. 2016).

Evaluation of CUR NEs prepared using MCT, canola oil or linseed oil as oil phases and stabilized by different emulsifiers (Tween 80, lecithin, whey protein isolate and acacia) with high pressure homogenization showed that the increase in oil phase concentration resulted in increased CUR content, particle size and viscosity of NE but decreased the stability that was pronouncedly affected if the stabilizing agent was lecithin; the maximum CUR content in NE was obtained using MCT as oil phase (Ma et al. 2017). Citral NE with mean particle size 467.83 nm produced using a mixture of gelatin and Tween 20 as emulsifiers in a ratio 3:1 (total emulsifier concentration of the emulsion system was 10 g/kg) remained stable during storage for 14 days at 30 °C and under acidic conditions it was able to protect citral from degradation and decreased the formation of off-flavor compounds (e.g. *p*-cymene, *p*-cresol and *p*-methylacetophenone) relative to a single emulsifier (Tian et al. 2017).

NEs containing *trans*-cinnamaldehyde as an active agent and 1,8-cineol as the Ostwald ripening inhibitor containing Tween 80 as emulsifier with surfactant to oil ratio of 2:1 (w/w) that were prepared using ultrasonic technology, exhibited notable stability for 6 months with considerably small particle size of 27.76±0.37 nm and superb antibacterial activity against *E. coli*, *S. aureus* and *Pseudomonas aeruginosa* and treatment with optimized NE caused dramatic increase of *E. coli*'s membrane fluidity (Moghimi et al. 2017).

Physical stabilities of droplets (344, 173, and 98 nm in diameter) of fucoxanthin NEs prepared using high-pressure microfluidizer and containing as the oil phase the structured lipid that enriched pinolenic acid at sn-2 position decreased with increases in the initial size and storage temperature, while fucoxanthin chemical stability was improved. The reduction of the digestion

stability of fucoxanthin NE with decreasing initial particle diameter could be probably attributed to the increased surface area interacting with pancreatic lipase with decreasing droplet size (Huang et al. 2017).

2.5.6 Nanoemulsions used in edible coatings

Fresh apples (Golab Kohanz) coated with 0.5% CS NE (<100 nm) pronouncedly reduced weight loss, respiration rate, ethylene production and peroxidase activity of the samples compared with the control, greatly affected polyphenol oxidase activity, slowed down softening process, maintained the quality of apples and also improved the flesh color after the climacteric peak (Gardesh et al. 2016). The combination of an antimicrobial edible coating on green beans consisting of modified CS containing a NE of mandarin EO with high hydrostatic pressure notably reduced *Listeria innocua* inoculated on green bean, while it also had a strong impact on green beans firmness during 14 days refrigerated storage at 4 °C (Donsi et al. 2015). The combined use of nanoemulsified lemon EO with modified CS resulted in the remarkable increase in antimicrobial activity, with respect to other EOs, whereby incorporation of nanoencapsulated lemon EO into the modified CS coating prolonged the shelf life of rucola leaves from 3 to 7 d, being more effective than a coating made of modified CS or EO alone (Sessa et al. 2015). Coating of silvery pomfret with citrus EO NEs based on CS NPs loaded EO ensured better preservation effects than coatings with conventional emulsion due to more efficient prevention against microorganisms and lipid oxidation (Wu et al. 2016).

Oleic acid NE as a part of starch-based edible coating suspensions, incorporated with a mixture of three natural antimicrobials: lactic acid, nisin, and lauric arginate may be used as coating to extend the shelf life of fresh foods (Sanchez-Ortega et al. 2016).

Grape berry (*Vitis labruscana* Bailey) coatings of lemongrass oil incorporating NE exhibited antimicrobial effects against *S. typhimurium* and *E. coli* 0157:H7 during storage at 4 and 25 °C for 28 days, they did not considerably alter the flavor of the berries, improved their glossiness, reduced losses of weight and prolong their shelf life (Kim et al. 2014b). The lemongrass oil/CS NE coating showed effectiveness in improving microbiological safety and preserving grape berries as well (Oh et al. 2017). A carnauba-shellac wax-based NE containing lemongrass oil prepared using high pressure homogenization and used for coating of 'Fuji' apples significantly improved the quality of apples during storage for 5 months compared to apples without coating (Jo et al. 2014). By mixing a carnauba wax-based solution (18%, w/w) with NE containing lemongrass oil coating for plums was developed, that was able to inhibit *S. typhimurium* and *E. coli* during storage, did not pronouncedly alter the flavor, fracturability, or glossiness of the plums, reduced weight loss and ethylene production and ensured higher firmness of coated plums compared to uncoated ones (Kim et al. 2013).

At 21 days of storage, polyphenol oxidase activity decreased by 65% in the fresh-cut Red Delicious apples coated with α-tocopherol NE (<200 nm; zeta potential < -40 mV, browning indexes of 43.5) and α-tocopherol NE with nopal mucilage (*Opuntia ficus indica*) (browning indexes of 39.3). As determining parameter in controlling texture and the browning index the particle size of the NE droplets could be considered and application of nopal mucilage helps control the browning index (Zambrano-Zaragoza et al. 2016).

NE-based edible coatings containing oregano EO and mandarin fiber were found to improve the shelf life of low-fat cut cheese (Artiga-Artigas et al. 2017). Orange peel EO (0.5 and 1.0%) ME and NE used in pectin-based coating to extend the shelf life of fresh-cut orange, maintained at 4 °C for 17days, notably reduced weight and ascorbic acid losses of coated samples as well as higher antibacterial and antifungal effects were estimated compared to control without changes in senzory parameters (Radi et al. 2018).

Taghavi et al. (2018) investigated the effects of the microfluidic pressure (600–1200 bar) and cycles (2–4) on the inhibitory activity and physicochemical properties of the NE loaded with a natural antibacterial mixture (i.e., citral, trans-2-hexen-1-ol, and linalool, 1:1:1 w/w) and found that in general the physicochemical properties of the antibacterial NE were affected by the cycle

to greater extent than by the pressure and the microfluidization condition did not considerably affect the antibacterial activity of the NE. Thus, the O/W emulsions could provide an adequate delivery system for these bioactive compounds.

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References

Abbas S, Hayat K, Karangwa E, Bashari M, Zhang XM (2013) An overview of ultrasound-assisted food-grade nanoemulsions. Food Eng Rev 5(3):139−157. doi:10.1007/s12393-013-9066-3

Abd E, Namjoshi S, Mohammed YH, Roberts MS, Grice JE (2016) Synergistic skin penetration enhancer and nanoemulsion formulations promote the human epidermal permeation of caffeine and naproxen. J Pharm Sci 105(1):212−220. doi:10.1002/jps.24699

Abd E, Benson HAE, Roberts MS, Grice JE (2018) Minoxidil skin delivery from nanoemulsion formulations containing eucalyptol or oleic acid: Enhanced diffusivity and follicular targeting. Pharmaceutics 10(1):19. doi:10.3390/pharmaceutics10010019

Abd-Elsalam KA, Khokhlov AR (2015) Eugenol oil nanoemulsion: antifungal activity against *Fusarium oxysporum* f. sp. *vasinfectum* and phytotoxicity on cottonseeds. Appl Nanosci 5:255–265. doi: 10.1007/s13204-014-0398-y

Abdou ES, Galhoum GF, Mohamed Entsar N (2018) Curcumin loaded nanoemulsions/pectin coatings for refrigerated chicken fillets. Food Hydrocoll 83:445–453. doi:10.1016/j.foodhyd.2018.05.026

Abu-Fayyad A, Nazzal S (2017) Gemcitabine-vitamin E conjugates: Synthesis, characterization, entrapment into nanoemulsions, and *in-vitro* deamination and antitumor activity. Int J Pharm 528(1-2):463−470. doi:10.1016/j.ijpharm.2017.06.031

Abu-Fayyad A, Kamal MM, Carroll JL, Dragoi AM, Cody R, Cardelli J, Nazzal S (2018) Development and *in-vitro* characterization of nanoemulsions loaded with paclitaxel/γ-tocotrienol lipid conjugates. Int J Pharm 536(1):146−157. doi:10.1016/j.ijpharm.2017.11.062

Achari GA, Kowshik M (2018) Recent developments on nanotechnology in agriculture: Plant mineral nutrition, health, and interactions with soil microflora. J Agric Food Chem 66(33):8647–8661. doi: 10.1021/acs.jafc.8b00691

Adjonu R, Doran G, Torley P, Agboola S (2014) Whey protein peptides as components of nanoemulsions: A review of emulsifying and biological functionalities. J Food Eng 122:15–27. DOI: 10.1016/j.jfoodeng.2013.08.034

Afzal SM, Shareef MZ, Dinesh T, Kishan V (2016a) Folate-PEG-decorated docetaxel lipid nanoemulsion for improved antitumor activity. Nanomedicine 11(16):2171–2184. doi:10.2217/nnm-2016-0120

Afzal SM, Naidu VD, Harishankar N, Kishan V (2016b) Albumin anchored docetaxel lipid nanoemulsion for improved targeting efficiency - preparation, characterization, cytotoxic, antitumor and *in vivo* imaging studies. Drug Deliv 23(4):1355−63. doi:10.3109/10717544.2015.1030715

Afzal SM, Shareef MZ, Kishan V (2016c) Transferrin tagged lipid nanoemulsion of docetaxel for enhanced tumor targeting. J Drug Deliv Sci Technol 36:175−182. doi:10.1016/j.jddst.2016.10.008

Agarwal V, Bajpai M, Sharma A (2018) Patented and approval scenario of nanopharmaceuticals with relevancy to biomedical application, manufacturing procedure and safety aspects. Recent Pat Drug Deliv Formul 12(1):40–52. doi:10.2174/1872211312666180105114644

Ahmad G, El Sadda R, Botchkina G, Ojima I, Egan J, Amiji M (2017) Nanoemulsion formulation of a novel taxoid DHA-SBT-1214 inhibits prostate cancer stem cell-induced tumor growth. Cancer Lett 406:71–80. doi:10.1016/j.canlet.2017.08.004

Ahmad N, Alam MA, Ahmad FJ, Sarafroz M, Ansari K, Sharma S, Amir M (2018a) Ultrasonication techniques used for the preparation of novel Eugenol-nanoemulsion in the treatment of wounds healings and anti-inflammatory. J Drug Deliv Sci Technol 46:461−473. doi:10.1016/j.jddst.2018.06.003

Ahmad U, Akhtar J, Singh SP, Badruddeen, Ahmad FJ, Siddiqui S, Wahajuddin (2018b) Silymarin nanoemulsion against human hepatocellular carcinoma: development and optimization. Artif Cells Nanomed Biotechnol 46(2):231–241. doi:10.1080/21691401.2017.1324465

Ahmed M, Smith DM, Hamouda T, Rangel-Moreno J, Fattom A, Khader SA (2017) A novel nanoemulsion vaccine induces mucosal Interleukin-17 responses and confers protection upon *Mycobacterium tuberculosis* challenge in mice. Vaccine 35(37):4983−4989. doi:10.1016/j.vaccine.2017.07.073

Akbas E, Soyler UB, Oztop MH (2017) Capsaicin emulsions: Formulation and characterization. J Dispers Sci Technol 38(8):1079−1086. doi:10.1080/01932691.2016.1224717

Akhter S, Anwar M, Siddiqui MA, Ahmad I, Ahmad J, Ahmad MZ, Bhatnagar A, Ahmad FJ (2016) Improving the topical ocular pharmacokinetics of an immunosuppressant agent with mucoadhesive nanoemulsions: Formulation development, *in-vitro* and *in-vivo* studies. Colloids Surf B Biointerfaces 148:19−29. doi:10.1016/j.colsurfb.2016.08.048

Aktar MW, Sengupta D, Chowdhury A (2009) Impact of pesticides use in agriculture: their benefits and hazards. Interdiscip Toxicol 2:1–12. doi: 10.2478/v10102-009-0001-7

Alarcon-Alarcon C, Inostroza-Riquelme M, Torres-Gallegos C, Araya C, Miranda M, Sanchez-Caamano JC, Moreno-Villoslada I, Oyarzun-Ampuero FA (2018) Protection of astaxanthin from photodegradation by its inclusion in hierarchically assembled nano and microstructures with potential as food. Food Hydrocoll 83:36–44. doi:10.1016/j.foodhyd.2018.04.033

Alexandre EMC, Lourenco RV, Bittante AMQB, Moraes ICF, Sobral PJD (2016) Gelatin-based films reinforced with montmorillonite and activated with nanoemulsion of ginger essential oil for food packaging applications. Food Packaging and Shelf Life 10:87–96. doi:10.1016/j.fpsl.2016.10.004

Al-Halafi AM (2014) Nanocarriers of nanotechnology in retinal diseases. Saudi J Ophthalmol 28(4):304−309. doi:10.1016/j.sjopt.2014.02.009

Ali EOM, Shakil NA, Rana VS, et al (2017) Antifungal activity of nano emulsions of neem and citronella oils against phytopathogenic fungi, *Rhizoctonia solani* and *Sclerotium rolfsii*. Ind Crops Prod 108:379–387. doi: 10.1016/j.indcrop.2017.06.061

Alkhatib MH, Binsiddiq BM, Backer WS (2017a) *In vivo* evaluation of the anticancer activity of a water-in-garlic oil nanoemulsion loaded docetaxel. Int. J Pharm Sci Rev Res 8(12):5373–5379. doi:10.13040/IJPSR.0975-8232.8(12).5373-79

Alkhatib MH, Alharbi SA, Mahassni SH (2017b) *In vivo* evaluation of the anticancer activity of the docetaxel incorporated into nanoemulsion based on orange oil. Pharmacophore 8(6):41–47

Alkhatib MH, Nori DA, Al-Ghamdi MA (2017c) Antitumor activity and hepatotoxicity effect of Sorafenib incorporated into nanoemulsion formulated with flaxseed oil running title: Antitumor activity and hepatotoxicity effect of Sorafenib. Int J Biol Pharm Allied Sci 6(1):175−188

Alkhatib MH, Al-Otaibi WA, Wali AN (2018a) Antineoplastic activity of mitomycin C formulated in nanoemulsions-based essential oils on HeLa cervical cancer cells. Chem Biol Interact 291:72−80. doi:10.1016/j.cbi.2018.06.009

Alkhatib MH, Alnahdi NS, Backer WS (2018b) Antitumor activity, hematotoxicity and hepatotoxicity of sorafenib formulated in a nanoemulsions based on the carrot seed oil. Int J Life Sci Biotechnol Pharma Res 8(1):50–57

Al-Otaibi WA, Alkhatib MH, Wali AN (2018) Cytotoxicity and apoptosis enhancement in breast and cervical cancer cells upon coadministration of mitomycin C and essential oils in nanoemulsion formulations. Biomed Pharmacother 106:946–955. doi:10.1016/j.biopha.2018.07.041

Alvarado HL, Abrego G, Souto EB, Garduno-Ramirez ML, Clares B, Garcia ML, Calpena AC (2015) Nanoemulsions for dermal controlled release of oleanolic and ursolic acids: *In vitro*, *ex vivo* and *in vivo* characterization. Colloids Surf B Biointerfaces 130:40−47. doi:10.1016/j.colsurfb.2015.03.062

Alzorqi I, Ketabchi MR, Sudheer S, Manickam S (2016) Optimization of ultrasound induced emulsification on the formulation of palm-olein based nanoemulsions for the incorporation of antioxidant β-D-glucan polysaccharides. Ultrason Sonochem 31:71−84. doi:10.1016/j.ultsonch.2015.12.004

Ansaril MJ, Ahmed MM, Anwer MK, Jamil S, Alalaiwe A, Alshetaili AS, Shdefat R, Ali R, Shakeel F (2017) Formulation and characterization of fluconazole loaded oil nanoemulsions. Indo Am J Pharm Sci 4(4):852−860. doi:10.5281/zenodo.804032

Anton N, Vandamme TF (2011) Nano-emulsions and micro-emulsions: Clarifications of the critical differences. Pharm Res 28:978–985. doi:10.1007/s11095-010-0309-1

Anton N, Akram S, Vandamme F (2018) Transitional nanoemulsification methods. Jafari SM, McClements DK (eds) Nanoemulsions Formulation, Applications, and Characterization, AP Academic Press (Elsevier), London, pp 77−100. https://doi.org/10.1016/B978-0-12-811838-2.00004-7

Aqil M, Kamran M, Ahad A, Imam SS (2016) Development of clove oil based nanoemulsion of olmesartan for transdermal delivery: Box-Behnken design optimization and pharmacokinetic evaluation. J Mol Liq 214:238−248. doi:10.1016/j.molliq.2015.12.077

Arancibia C, Riquelme N, Zuniga R, Matiacevich S (2017) Comparing the effectiveness of natural and synthetic emulsifiers on oxidative and physical stability of avocado oil-based nanoemulsions. Innov Food Sci Emerg Technol 44:159–166. doi:10.1016/j.ifset.2017.06.009

Arbain NH, Salim N, Masoumi HRF, Wong TW, Basri M, Abdul Rahman MB (2018) *In vitro* evaluation of the inhalable quercetin loaded nanoemulsion for pulmonary delivery. Drug Deliv Transl Res. doi:10.1007/s13346-018-0509-5

Argenta DF, de Mattos CB, Misturini FD, Koester LS, Bassani VL, Simoes, CMO, Teixeira HF (2014) Factorial design applied to the optimization of lipid composition of topical antiherpetic nanoemulsions containing isoflavone genistein. Int J Nanomedicine 9:4737−4747. doi:10.2147/IJN.S67732

Argenta DF, Bidone J, Misturini FD, Koester LS, Bassani VL, Simoes CMO, Teixeira HF (2016) *In vitro* evaluation of mucosa permeation/retention and antiherpes activity of genistein from cationic nanoemulsions. J Nanosci Nanotechnol 16(2):1282−1290. doi:10.1166/jnn.2016.11676

Artiga-Artigas M, Acevedo-Fani A., and Martin-Belloso O (2017) Improving the shelf life of low-fat cut cheese using nanoemulsion-based edible coatings containing oregano essential oil

and mandarin fiber. Food Control 76:1–12. doi:10.1016/j.foodcont.2017.01.001

Artiga-Artigas M, Guerra-Rosas MI, Morales-Castro J, Salvia-Trujillo L, Martin-Belloso O (2018) Influence of essential oils and pectin on nanoemulsion formulation: A ternary phase experimental approach. Food Hydrocoll 81:209–219. doi:10.1016/j.foodhyd.2018.03.001

Assadpour E, Maghsoudlou Y, Jafari SM, Ghorbani M, Aalami M (2016) Evaluation of folic acid nano-encapsulation by double emulsions. Food Bioprocess Tech 9(12):2024–2032. doi:10.1007/s11947-016-1786-y

Attia MF, Dieng SM, Collot M, Klymchenko AS, Bouillot C, Serra CA, Schmutz M, Er-Rafik M, Vandamme TF, Anton N (2017) Functionalizing nanoemulsions with carboxylates: Impact on the biodistribution and pharmacokinetics in mice. Macromol Biosci 17(7):1600471. doi:10.1002/mabi.201600471

Ayoub AM, Ibrahim MM, Abdallah MH, Mandy MA (2016) Sulpiride microemulsions as antipsychotic nasal drug delivery systems: In-vitro and pharmacodynamic study. J Drug Deliv Sci Technol 36:10−22. doi:10.1016/j.jddst.2016.09.002

Back PI, Furtado KR, Nemitz MC, Balestrin LA, Fachel FNS, Gomes HM, Schuh RS, Moreira JC, von Poser GL, Teixeira HF (2018) Skin permeation and oxidative protection effect of soybean isoflavones from topical nanoemulsions - A comparative study of extracts and pure compounds. AAPS PharmSciTech. doi:10.1208/s12249-018-1133-x

Badawy ME, Saad ASA, Tayeb EHM, Mohammed SA, Abd-Elnabi AD (2017) Optimization and characterization of the formation of oil-in-water diazinon nanoemulsions: Modeling and influence of the oil phase, surfactant and sonication. J Environ Sci Health B 52(12):896-911. doi: 10.1080/03601234.2017.1362941

Baghbani F, Mortarzadeh F (2017) Bypassing multidrug resistant ovarian cancer using ultrasound responsive doxorubicin/curcumin co-deliver alginate nanodroplets. Colloids Surf B Biointerfaces 153:132−140. doi:10.1016/j.colsurfb.2017.01.051

Baghbani F, Chegeni M, Mortarzadeh F, Hadian-Ghazvini S, Raz M (2017) Novel ultrasound-responsive chitosan/perfluorohexane nanodroplets for image-guided smart delivery of an anticancer agent: Curcumin. Mater Sci Eng C Mater Biol Appl 74:186−193. doi:10.1016/j.msec.2016.11.107

Bai L, McClements DJ (2016) Development of microfluidization methods for efficient production of concentrated nanoemulsions: Comparison of single- and dual-channel microfluidizers. J Colloid Interface Sci 466:206−212. doi:10.1016/j.jcis.2015.12.039

Bai L, Huan SQ, Gu JY, McClements DJ (2016) Fabrication of oil-in-water nanoemulsions by dual-channel microfluidization using natural emulsifiers: Saponins, phospholipids, proteins, and polysaccharides. Food Hydrocoll 61:703−711. doi:10.1016/j.foodhyd.2016.06.035

Balestrin LA, Bidone J, Bortolin RC, Moresco K, Moreira JC, Teixeira HF (2016) Protective effect of a hydrogel containing *Achyrocline satureioides* extract-loaded nanoemulsion against UV-induced skin damage. J Photochem Photobiol B 163:269−276. doi:10.1016/j.jphotobiol.2016.08.039

Barradas TN, Senna JP, Cardoso SA, Nicoli S, Padula C, Santi P, Rossi F, Silva KGDE, Mansur CRE (2017) Hydrogel-thickened nanoemulsions based on essential oils for topical delivery of psoralen: Permeation and stability studies. Eur J Pharm Biopharm 116:38−50. doi:10.1016/j.ejpb.2016.11.018

Bhattacharyya A, Duraisamy P, Govindarajan M, Buhroo AA, Prasad R (2016) Nano-biofungicides: Emerging trend in insect pest control. In: Advances and Applications through Fungal Nanobiotechnology (ed. Prasad R), Springer International Publishing Switzerland 307-319

Bhushan B, Luo D, Schricker SR, Sigmund W, Zauscher S (Eds) (2014) Handbook of nanomaterials properties, Springer, Berlin-Heidelberg

Bonferoni MC, Riva F, Invernizzi A, Dellera E, Sandri G, Rossi S, Marrubini G, Bruni G, Vigani B, Caramella C, Ferrari F (2018) Alpha tocopherol loaded chitosan oleate nanoemulsions for wound healing. Evaluation on cell lines and *ex vivo* human biopsies, and stabilization in spray dried Trojan microparticles. Eur J Pharm Biopharm 123:31−41. doi:10.1016/j.ejpb.2017.11.008

Bovi GG, Petrus RR, Pinho SC (2017) Feasibility of incorporating buriti (*Mauritia flexuosa* L.) oil nanoemulsions in isotonic sports drink. Int J Food Sci Technol 52(10):2201−2209. doi:10.1111/ijfs.13499

Brownlow B, Nagaraj VJ, Nayel A, Joshi M, Elbayoumi T (2015) Development and *in vitro* evaluation of vitamin E-enriched nanoemulsion vehicles loaded with genistein for

chemoprevention against UVB-induced skin damage. J Pharm Sci 104(10):3510−3523. doi:10.1002/jps.24547

Camara ALD, Nagel G, Tschiche HR, Cardador CM, Muehlmann LA, de Oliveira DM, Alvim PQ, Azevedo RB, Calderon M, Longo JPF (2017) Acid-sensitive lipidated doxorubicin prodrug entrapped in nanoemulsion impairs lung tumor metastasis in a breast cancer model. Nanomedicine 12(15):1751−1765. doi:10.2217/nnm-2017-0091

Campos EVR, de Oliveira JL, Pascoli M, et al (2016) Neem oil and crop protection: From now to the future. Front Plant Sci 7:1494. doi: 10.3389/fpls.2016.01494

Campos EVR, Proença PLF, Oliveira JL, et al (2018) Use of botanical insecticides for sustainable agriculture: Future perspectives. Ecol Indic. doi: 10.1016/j.ecolind.2018.04.038

Carvalho VFM, Migotto A, Giacone DV, de Lemos DP, Zanoni TB, Maria-Engler SS, Costa-Lotufo LV, Lopes LB (2017) Co-encapsulation of paclitaxel and C6 ceramide in tributyrin-containing nanocarriers improve co-localization in the skin and potentiate cytotoxic effects in 2D and 3D models. Eur J Pharm 109:131−143. doi:10.1016/j.ejps.2017.07.023

Chang YH, McLandsborough L, McClements DJ (2012) Physical properties and antimicrobial efficacy of thyme oil nanoemulsions: Influence of ripening inhibitors. J Agric Food Chem 60(48):12056-12063. doi:10.1021/jf304045a

Chellaram C, Murugaboopathi G, John AA, Sivakumar R, Ganesan S, Krithika S, Priya G (2014) Significance of nanotechnology in food industry. APCBEE Procedia 8:109−113. doi:10.1016/j.apcbee.2014.03.010

Cheong AM, Nyam KL (2016) Improvement of physical stability of kenaf seed oil-in-water nanoemulsions by addition of β-cyclodextrin to primary emulsion containing sodium caseinate and Tween 20. J Food Eng 183:24−31. doi:10.1016/j.jfoodeng.2016.03.012

Cheong AM, Tan CP, Nyam KL (2016) *In vitro* evaluation of the structural and bioaccessibility of kenaf seed oil nanoemulsions stabilised by binary emulsifiers and β-cyclodextrin complexes. J Food Eng 189:90−98. doi:10.1016/j.jfoodeng.2016.06.002

Chin C-P, Lan C-W, Wu H-S (2012) Application of biodiesel as carrier for insecticide emulsifiable concentrate formulation. J Taiwan Inst Chem Eng 43:578–584. doi: 10.1016/j.jtice.2012.02.003

Choudhury H, Gorain B, Pandey M, Chatterjee LA, Sengupta P, Das A, Molugulu N, Kesharwani P (2017) Recent update on nanoemulgel as topical drug delivery system. J Pharm Sci 106(7):1736−1751. doi:10.1016/j.xphs.2017.03.042

Choupanian M, Omar D, Basri M, Asib N (2017) Preparation and characterization of neem oil nanoemulsion formulations against *Sitophilus oryzae* and *Tribolium castaneum* adults. J Pest Sci 42:158–165. doi: 10.1584/jpestics.D17-032

Ciocci M, Iorio E, Carotenuto F, Khashoggi HA, Nanni F, Melino S (2016) H_2S-releasing nanoemulsions: a new formulation to inhibit tumor cells proliferation and improve tissue repair. Oncotarget 7(51):84338−84358. doi:10.18632/oncotarget.12609

Cordoba JPL, Sobral, PJA (2017) Physical and antioxidant properties of films based on gelatin, gelatin-chitosan or gelatin-sodium caseinate blends loaded with nanoemulsified active compounds. J Food Eng 213:47−53. doi:10.1016/j.jfoodeng.2017.05.023

Dammak I, de Carvalho RA, Trindade CSF, Lourenco RV, Sobral PJD (2017) Properties of active gelatin films incorporated with rutin-loaded nanoemulsions. Int J Biol Macromol 98:39−49, doi:10.1016/j.ijbiomac.2017.01.094

de Matos RPA, Calmon MF, Amantino CF, Villa LL, Primo FL, Tedesco AC, Rahal P (2018) Effect of curcumin-nanoemulsion associated with photodynamic therapy in cervical carcinoma cell lines. Biomed Res Int 2018:4057959. doi:10.1155/2018/4057959

de Souza ML, Oliveira DD, Pereira NP, Soares DM (2018) Nanoemulsions and dermatological diseases: contributions and therapeutic advances. Int J Dermatol 57(8):894−900. doi:10.1111/ijd.14028

Díaz-Blancas V, Medina D, Padilla-Ortega E, Bortolini-Zavala R, Olvera-Romero M, Luna-Bárcenas G (2016) Nanoemulsion formulations of fungicide Tebuconazole for agricultural applications. Molecules 21:1271. doi: 10.3390/molecules21101271

Dolez PI (2015) Nanoengineering: Global approaches to health and safety issues. Elsevier, Amterdam

Donsi F, Marchese E, Maresca P, Pataro G, Vu DK, Salmieri, S, Lacroix M, Ferrari G (2015) Green beans preservation by combination of a modified chitosan based-coating containing nanoemulsion of mandarin essential oil with high pressure or pulsed light processing. Postharvest Biol Technol 106:21–32. doi:10.1016/j.postharvbio.2015.02.006

Donsi F, Ferrari G (2016) Essential oil nanoemulsions as antimicrobial agents in food. J Biotechnol 233:106–120. doi:10.1016/j.jbiotec.2016.07.005

Doost AS, Devlieghere F, Dirckx A, Van der Meeren P (2018) Fabrication of *Origanum compactum* essential oil nanoemulsions stabilized using Quillaja Saponin biosurfactant. J Food Process Preserv 42(7):e13668. doi:10.1111/jfpp.13668

Du Z, Wang C, Tai X, Wang GY, Liu XY (2016) Optimization and characterization of biocompatible oil-in-water nanoemulsion for pesticide delivery. ACS Sustain Chem Eng 4(3):983–991. doi: 10.1021/acssuschemeng.5b01058

Esquerdo VM, Silva PP, Dotto GL, Pinto LAA (2018) Nanoemulsions from unsaturated fatty acids concentrates of carp oil using chitosan, gelatin, and their blends as wall materials. Eur J Lipid Sci Technol 120(2):1700240. doi:10.1002/ejlt.201700240

Fachel FNS, Medeiros-Neves B, Dal Pra M, Schuh RS, Veras KS, Bassani VL, Koester LS, Henriques AT, Braganhol E, Teixeira HF (2018) Box-Behnken design optimization of mucoadhesive chitosan-coated nanoemulsions for rosmarinic acid nasal delivery-*In vitro* studies. Carbohydr Polym 199:572–582. doi:10.1016/j.carbpol.2018.07.054

Feng J, Shi Y, Yu Q, Sun CC, Yang GT (2016) Effect of emulsifying process on stability of pesticide nanoemulsions. Colloids Surf A Physicochem Eng Asp 497:286–292. doi: 10.1016/j.colsurfa.2016.03.024

Fernandes CP, de Almeida FB, Silveira AN, Gonzalez MS, Mello CB, Feder D, Apolinário R, Santos MG, Carvalho JC, Tietbohl LA, Rocha L, Falcão DQ (2014) Development of an insecticidal nanoemulsion with *Manilkara subsericea* (Sapotaceae) extract. J Nanobiotechnology 12:22. doi: 10.1186/1477-3155-12-22

Fountain ED, Wratten SD (2013) Conservation biological control and biopesticides in agricultural. In: Reference module in earth systems and environmental sciences, Elsevier, doi:10.1016/B978-0-12-409548-9.00539-X

Furtado CDM, de Faria, FSEV, Azevedo RB, Py-Daniel K, Camara ALD, da Silva JR, Oliveira ED, Rodriguez AFR, Degterev IA (2017) *Tectona grandis* leaf extract, free and associated with nanoemulsions, as a possible photosensitizer of mouse melanoma B16 cell. J Photochem Photobiol B 167:242–248. doi:10.1016/j.jphotobiol.2017.01.004

Gadkari PV, Shashidhar MG, Balaraman M (2017) Delivery of green tea catechins through oil-in-water (O/W) nanoemulsion and assessment of storage stability. J Food Eng 99:65–76. doi:10.1016/j.jfoodeng.2016.12.009

Gallarate M, Chirio D, Bussano R, Peira E, Battaglia L, Baratta F, Trotta M (2013) Development of O/W nanoemulsions for ophthalmic administration of timolol. Int J OF Pharm 440(2):126−134. doi:10.1016/j.ijpharm.2012.10.015

Ganta S, Talekar M, Singh A, Coleman TP, Amiji MM (2014) Nanoemulsions in translational research-opportunities and challenges in targeted cancer therapy. AAPS PharmSciTech 15(3): 694–708. doi:10.1208/s12249-014-0088-9

Ganta S, Singh A, Rawal Y, Cacaccio J, Patel NR, Kulkarni P, Ferris CF, Amiji MM, Coleman TP (2016) Formulation development of a novel targeted theranostic nanoemulsion of docetaxel to overcome multidrug resistance in ovarian cancer. Drug Deliv 23(3):968–980. doi: 10.3109/10717544.2014.923068

Gao YY, Cheng XJ, Wang ZG, Wang J, Gao TT, Li P, Kong M, Chen XG (2014) Transdermal delivery of 10,11-methylenedioxycamptothecin by hyaluronic acid based nanoemulsion

for inhibition of keloid fibroblast. Carbohydr Polym 112:376−386. doi:10.1016/j.carbpol.2014.05.026

Gardesh ASK, Badii F, Hashemi M, Ardakani AY, Maftoonazad N, Gorji AM (2016) Effect of nanochitosan based coating on climacteric behavior and postharvest shelf-life extension of apple cv. Golab Kohanz. LWT-Food Sci Technol 70:33–40. doi:10.1016/j.lwt.2016.02.002

Geng TY, Xu C, Xu GH (2016) Albumin conjugated lipid nanoemulsion for site specific delivery of rapamycin at inflammatory site of spinal cord injury. Int J Clin Exp Med 9(11):21028–21037. doi:10.1208/s12249-017-0867-1

Gharibzahedi SMT (2017) Ultrasound-mediated nettle oil nanoemulsions stabilized by purified jujube polysaccharide: Process optimization, microbial evaluation and physicochemical storage stability. J Mol Liq 234:240–248. doi:10.1016/j.molliq.2017.03.094

Ghosh V, Mukherjee A, Chandrasekaran N (2013) Ultrasonic emulsification of food-grade nanoemulsion formulation and evaluation of its bactericidal activity. Ultrason Sonochem 20(1):338–344. doi:10.1016/j.ultsonch.2012.08.010

Gupta A, Eral HB, Hatton TA, Doyle PS (2016) Nanoemulsions: formation, properties and applications. Soft Matter 12(11):2826–2841. doi:10.1039/c5sm02958a

Habibi K, Sepehri H, Delphi L, Mirjalili MH, Rafati H (2017) Design and production of methyl jasmonate nanoemulsions using experimental design technique and evaluation of its anti-cancer efficacy. Pharmazie 72(11):652−662. doi:10.1691/ph.2017.7078

Hadžiabdić J, Orman D, Elezović A, Vranić E, Rahić O (2017) Preparation of nanoemulsions by high-energy and lowenergy emulsification methods. In A. Badnjevic (ed), CMBEBIH 2017, IFMBE Proceedings 62, Springer Nature Singapore Pte Ltd, pp 317−322. doi:10.1007/978-981-10-4166-2_48

Håkansson A, Rayner M (2018) General principles of nanoemulsion formation by high-energy mechanical methods. In: Jafari SM, McClements DK (eds) Nanoemulsions Formulation, Applications, and Characterization, AP Academic Press (Elsevier), London, 103−139. https://doi.org/10.1016/B978-0-12-811838-2.00005-9

Haron DEM, Chik Z, Noordin MI, Mohamed Z (2015) *In vitro* and *in vivo* evaluation of a novel testosterone transdermal delivery system (TTDS) using palm oil base. Iran J Basic Med Sci 18(12):1167−1175

Harwansh RK, Patra KC, Pareta SK, Singh J, Rahman MA (2011) Nanoemulsions as vehicles for transdermal delivery of glycyrrhizin. Braz. J. Pharm. Sci 47(4):769−778. doi:10.1590/S1984-82502011000400014

Harwansh RK, Mukherjee PK, Kar A, Bahadur S, Al-Dhabi NA, Duraipandiyan V (2016) Enhancement of photoprotection potential of catechin loaded nanoemulsion gel against UVA induced oxidative stress. J Photochem Photobiol B 160:318−329. doi:10.1016/j.jphotobiol.2016.03.026

Hashem AS, Awadalla SS, Zayed GM, Maggi F, Benelli G (2018) *Pimpinella anisum* essential oil nanoemulsions against *Tribolium castaneum*—insecticidal activity and mode of action. Environ Sci Pollut Res 25(19):18802–18812. doi: 10.1007/s11356-018-2068-1

Hayles J, Johnson L, Worthley C, Losic D (2017) Nanopesticides: a review of current research and perspectives. In: In: Grumezescu AM (ed) New pesticides and soil sensors in Nanotechnology in the agri-food industry, Vol. 10, Elsevier, London, UK, 193–225

Hazra DK, Karmakar R, Poi R, Bhattacharya S, Mondal S (2017) Recent advances in pesticide formulations for eco-friendly and sustainable vegetable pest management: A review. AAES 2(3):232–237. doi: 10.13140/rg.2.2.30036.91527

Hazrati H, Saharkhiz MJ, Niakousari M, Moein M (2017) Natural herbicide activity of *Satureja hortensis* L. essential oil nanoemulsion on the seed germination and morphophysiological features of two important weed species. Ecotox Environ Saf 142:423–430. doi: 10.1016/j.ecoenv.2017.04.041

Hemraj C (2017) Nanopesticide: Current status and future possibilities. ARTOAJ 5(1):555651. doi: 10.19080/ARTOAJ.2017.05.555651

Hernandez-Hernandez E, Lira-Moreno CY, Guerrero-Legarreta I, Wild-Padua G, Di Pierro P, Garcia-Almendarez BE, Regalado-Gonzalez C (2017) Effect of nanoemulsified and microencapsulated Mexican oregano (*Lippia graveolens* Kunth) essential oil coatings on quality of fresh pork meat. J Food Sci 82(6):1423−1432. doi:10.1111/1750-3841.13728

Hong L, Zhou CL, Chen FP, Han D, Wang CY, Li JX, Chi Z, Liu, CG (2017) Development of a carboxymethyl chitosan functionalized nanoemulsion formulation for increasing aqueous solubility, stability and skin permeability of astaxanthin using low-energy method. J Microencapsul 34(8):707−721. doi:10.1080/02652048.2017.1373154

Hou L, Liu Q, Shen LM, Liu Y, Zhang XQ, Chen FQ, Huang L (2018) Nano-delivery of fraxinellone remodels tumor microenvironment and facilitates therapeutic vaccination in desmoplastic melanoma. Theranostics 8(14):3781−3796. doi:10.7150/thno.24821

Huang ZH, Xu LQ, Zhu XM, Hu JN, Peng HL, Zeng ZL, Xiong H (2017) Stability and bioaccessibility of fucoxanthin in nanoemulsions prepared from pinolenic acid-contained structured lipid. Int J Food Eng 13(1):20160273. doi:10.1515/ijfe-2016-0273

Huang J, Wang Q, Li T, Xia N, Xia Q (2018) Multilayer emulsions as a strategy for linseed oil and α-lipoic acid micro-encapsulation: study on preparation and *in vitro* characterization. J Sci Food Agric 98(9):3513−3523. doi:10.1002/jsfa.8870

Hwang JY, Ha HK, Lee MR, Kim JW, Kim HJ, Lee WJ (2017) Physicochemical property and oxidative stability of whey protein concentrate multiple nanoemulsion containing fish oil. J Food Sci 82(2):437−444. doi:10.1111/1750-3841.13591

Iqbal B, Ali J, Baboota S (2018) Recent advances and development in epidermal and dermal drug deposition enhancement technology. Int J Dermatol 57(6):646−660. doi:10.1111/ijd.13902

Jaiswal M, Dudhe R, Sharma PK (2015) Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech 5:123−127. doi:10.1007/s13205-014-0214-0

Jampílek J, Brychtová K (2012) Azone analogues: Classification, design, and transdermal penetration principles. *Med Res Rev* 32(5):907−947. doi: 10.1002/med.20227

Jampílek J, Kráľová K (2015a) Application of nanotechnology in agriculture and food industry, its prospects and risks. Ecol Chem Eng S 22(3):321−361. doi:10.1515/eces-2015-0018

Jampílek J, Záruba Kamil, Oravec M, Kuneš M, Babula P, Ulbrich P, Breyinová I, Tříska J, Suchý P (2015b). Preparation of silica nanoparticles loaded with nootropics and their *in vivo* permeation through blood–brain barrier. Biomed Res Int 2015:812673

Jampílek J, Kráľová K (2017a) Nanopesticides: Preparation, targeting and controlled release. In: Grumezescu AM (ed) New pesticides and soil sensors in Nanotechnology in the agri-food industry, Vol. 10. Elsevier, London, UK, Chapter 3, 81-127. http://dx.doi.org/10.1016/B978-0-12-804299-1.00004-7

Jampílek J, Kráľová K (2017b) Nano-antimicrobials: Activity, benefits and weaknesses. In: Ficai A, Grumezescu AM (eds) Nanostructures in therapeutic medicine, Vol. 2 – Nanostructures for antimicrobial therapy. Elsevier, Amsterdam, The Netherlands, Chapter 2, 23-54. http://dx.doi.org/10.1016/B978-0-323-46152-8.00002-0

Jampílek J, Kráľová K (2017c) Nanomaterials for delivery of nutrients and growth-promoting compounds to plants. In: Prasad R, Kumar M, Kumar V (eds.) Nanotechnology: An agricultural paradigm. Springer, Singapore, Chapter 9, 177-226. doi:10.1007/978-981-10-4573-8_9

Jampílek J, Kráľová K (2018a) Application of nanobioformulations for controlled release and targeted biodistribution of drugs. In: Sharma AK, Keservani RK, Kesharwani RK (eds) Nanobiomaterials: Applications in drug delivery. CRC Press, Warentown, NJ, USA, Part II, Chapter 5, 131-208.

Jampílek J, Kráľová K (2018b) Nanomaterials applicable in food protection. In: Rai RV, Bai JA (eds) Nanotechnology applications in food industry. CRC Press/Taylor & Francis Group, Boca Raton, Chapter 5, 75–96.

Jampílek J, Kráľová K (2018c) Benefits and potential risks of nanotechnology applications in crop protection. In: And-Elsalam K, Prasad R (eds) Nanobiotechnology applications in

plant protection. Springer, Cham, Germany, Chapter 8, 189–246. doi:10.1007/978-3-319-91161-8_8

Jampílek J, Kráľová K (2019a) Nano-biopesticides in agriculture: State of art and future opportunities. In: Opender Koul (ed) Nano-Biopesticides today and future perspectives. Elsevier, in press

Jampílek J, Kráľová K (2019b) Recent advances in lipid nanocarriers applicable in the fight against cancer. In: Grumezescu AM (ed) Nanoarchitectonics in biomedicine – Recent progress of nanoarchitectonics in biomedical science. Elsevier, Amsterdam, The Netherlands, Chapter 10, in press.

Jampílek J, Kráľová K (2019c) Natural biopolymeric nanoformulations for brain drug delivery. In: Keservani RK, Sharma AK, Kesharwani RK (eds) Nanocariers for brain targeting. Principles and applications. CRC Press, Warentown, NJ, USA, Chapter 5, in press. http://appleacademicpress.com/nanocarriers-for-brain-targeting-principles-and-applications/9781771887304

Jo YJ, Kwon YJ (2014) Characterization of β-carotene nanoemulsions prepared by microfluidization technique. Food Sci Biotechnol 23(1):107−113. doi:10.1007/s10068-014-0014-7

Jo WS, Song HY, Song NB, Lee JH, Min SC, Song KB (2014) Quality and microbial safety of 'Fuji' apples coated with carnauba-shellac wax containing lemongrass oil. LWT-Food Sci Technol 55(2):490–497. doi:10.1016/j.lwt.2013.10.034

Joung HJ, Choi MJ, Kim JT, Park SH, Park HJ, Shin GH (2016) Food beverage system: Antioxidant property and *in vitro* digestion. J Food Sci 81(3):N745–N753. doi:10.1111/1750-3841.13224

Kaci M, Belhaffef A, Meziane S, Dostert G, Menu P, Velot E, Desobry S, Arab-Tehrany E (2018) Nanoemulsions and topical creams for the safe and effective delivery of lipophilic antioxidant coenzyme Q10. Colloids Surf B Biointerfaces 167:165–175. doi:10.1016/j.colsurfb.2018.04.010

Kah M, Walch H, Hofmann T (2018) Environmental fate of nanopesticides: durability, sorption and photodegradation of nanoformulated clothianidin. Environ Sci Nano 5(4):882–889. doi: 10.1039/C8EN00038G

Katzer T, Chaves P, Bernardi A, Pohlmann AR, Guterres SS, Beck RCR (2014) Castor oil and mineral oil nanoemulsion: development and compatibility with a soft contact lens. Pharm Dev Technol 19(2):232−237. doi:10.3109/10837450.2013.769569

Kaur K, Kumar R, Mehta SK (2016) Formulation of saponin stabilized nanoemulsion by ultrasonic method and its role to protect the degradation of quercitin from UV light. Ultrason Sonochem 31:29–38. doi:10.1016/j.ultsonch.2015.11.017

Kaur K, Kaur J, Kumar R, Mehta SK (2017) Formulation and physiochemical study of α-tocopherol based oil in water nanoemulsion stabilized with non toxic, biodegradable surfactant: Sodium stearoyl lactate. Ultrason Sonochem 38:570–578. doi:10.1016/j.ultsonch.2016.08.026

Khan I, Bahuguna A, Bhardwaj M, Pal Khaket T, Kang SC (2018) Carvacrol nanoemulsion evokes cell cycle arrest, apoptosis induction and autophagy inhibition in doxorubicin resistant-A549 cell line. Artif Cells Nanomed Biotechnol-in press. doi:10.1080/21691401.2018.1434187

Kim IH, Lee H, Kim JE, Song KB, Lee YS, Chung DS, Min SC (2013) Plum coatings of lemongrass oil-incorporating carnauba wax-based nanoemulsion. J Food Sci 78(10):E1551–E1559. doi:10.1111/1750-3841.12244

Kim JH, Ko JA, Kim JT, Cha DS, Cho JH, Park HJ, Shin GH (2014a) Preparation of a capsaicin-loaded nanoemulsion for improving skin penetration. J Agric Food Chem 62(3):725−732. doi:10.1021/jf404220n

Kim IH, Oh YA, Lee H, Bin Song K, Min SC (2014b) Grape berry coatings of lemongrass oil-incorporating nanoemulsion. LWT-Food Sci Technol 58(1):1−10. doi:10.1016/j.lwt.2014.03.018

Kim JE, Park YJ (2017a) Improved antitumor efficacy of hyaluronic acid-complexed paclitaxel nanoemulsions in treating non-small cell lung cancer. Biomol Ther 25(4):411−416. doi:10.4062/biomolther.2016.261

Kim JE, Park YJ (2017b) High paclitaxel-loaded and tumor cell-targeting hyaluronan-coated nanoemulsions. Colloids Surf B Biointerfaces 150:362−372. doi:10.1016/j.colsurfb.2016.10.050

Knowles A (2008) Recent developments of safer formulations of agrochemicals. Environmentalist 28:35–44. doi: 10.1007/s10669-007-9045-4

Komaiko J, McClements DJ (2015) Low-energy formation of edible nanoemulsions by spontaneous emulsification: Factors influencing particle size. J Food Eng 146:122−128. doi:10.1016/j.jfoodeng.2014.09.003

Kumar M, Misra A, Pathak K (2009) Formulation and characterization of nanoemulsion of olanzapine for intranasal delivery. PDA J Pharm Sci Technol 63(6):501−511

Kumar D, Ali J, Baboota S (2016) Omega 3 fatty acid-enriched nanoemulsion of thiocolchicoside for transdermal delivery: formulation, characterization and absorption studies. Drug Deliv 23(2):591−600. doi:10.3109/10717544.2014.916764

Kumari S, Kumaraswamy RV, Choudhary RC, Sharma SS, Pal A, Raliya R, Biswas P, Saharan V (2018) Thymol nanoemulsion exhibits potential antibacterial activity against bacterial pustule disease and growth promotory effect on soybean. Sci Rep 8:6650. doi:10.1038/s41598-018-24871-5

Lalu L, Tambe V, Pradhan D, Nayak K, Bagchi S, Maheshwari R, Kalia K, Tekade RK (2017) Novel nanosystems for the treatment of ocular inflammation: Current paradigms and future research directions. J Control Release 268:19−39. doi:10.1016/j.jconrel.2017.07.035

Lee WD, Liang YJ, Chen BH (2016) Effects of tanshinone nanoemulsion and extract on inhibition of lung cancer cells A549. Nanotechnology 27(49):495101. doi:10.1088/0957-4484/27/49/495101

Le Kim TH, Jun H, Kim JH, Park K, Kim JS, Nam YS (2017) Lipiodol nanoemulsions stabilized with polyglycerol-polycaprolactone block copolymers for theranostic applications. Biomater Res 21, 21 pages. doi:10.1186/s40824-017-0108-4

Leng P, Zhang Z, Li Q, et al (2014) Microemulsion formulation of carbendazim and its *in vitro* antifungal activities evaluation. PLoS ONE 9:e109580. doi: 10.1371/journal.pone.0109580

Li M, Zhu LF, Liu BM, Du LN, Jia XD, Han L, Jin YG (2016a) Tea tree oil nanoemulsions for inhalation therapies of bacterial and fungal pneumonia. Colloids Surf B Biointerfaces 141:408−416. doi:10.1016/j.colsurfb.2016.02.017

Li X, Mueller RH, Keck CM, Bou-Chacra NA (2016b) Mucoadhesive dexamethasone acetate-polymyxin B sulfate cationic ocular nanoemulsion - novel combinatorial formulation concept. Pharmazie 71(6):327−333. doi:10.1691/ph.2016.5190

Li YC, Zhong G, Meng FB, Yu H, Liu DY, Peng LX (2018) Konjac glucomannan octenyl succinate (KGOS) as an emulsifier for lipophilic bioactive nutrient encapsulation. J Sci Food Agric. doi:10.1002/jsfa.9122

Lim CJ, Basri M, Omar D, Abdul Rahman MB, Salleh AB, Raja Abdul Rahman RN (2013) Green nanoemulsion-laden glyphosate isopropylamine formulation in suppressing creeping foxglove (*A. gangetica*), slender button weed (*D. ocimifolia*) and buffalo grass (*P. conjugatum*): Glyphosate isopropylamine formulation for suppressing various weed species. Pest Manag Sci 69:104–111. doi: 10.1002/ps.3371

Lim C, Kim DW, Sim T, Hoang NH, Lee JW, Lee ES, Youn YS, Oh KT (2016) Preparation and characterization of a lutein loading nanoemulsion system for ophthalmic eye drops. J Drug Deliv Sci Technol 36:168−174. doi:10.1016/j.jddst.2016.10.009

Liu Y, Wei F, Wang Y, Zhu G (2011) Studies on the formation of bifenthrin oil-in-water nano-emulsions prepared with mixed surfactants. Colloids Surf A Physicochem Eng Asp 389:90–96. doi: 10.1016/j.colsurfa.2011.08.045

Liu CH, Huang HY (2012) Antimicrobial activity of curcumin-loaded myristic acid microemulsions against *Staphylococcus epidermidis*. Chem Pharm Bull 60(9):1118−1124. doi:10.1248/cpb.c12-00220

Liu CH, Lai KY, Wu WC, Chen YJ, Lee WS, Hsu CY (2015a) *In vitro* scleral lutein distribution by cyclodextrin containing nanoemulsions. Chem Pharm Bull 63(2):59-67. doi:10.1248/cpb.c14-00318

Liu YQ, Hou ZQ, Yang J, Gao YX (2015b) Effects of antioxidants on the stability of β-carotene in O/W emulsions stabilized by gum arabic. J Food Sci Tech-Mys 52(6):3300–3311. DOI: 10.1007/s13197-014-1380-0

Liu XJ, McClements DJ, Cao Y, Xiao H (2016) Chemical and physical stability of astaxanthin-enriched emulsion-based delivery systems. Food Biophys 11(3):302–310. doi:10.1007/s11483-016-9443-6

Liu Y, Yu XM, Sun RJ, Pan XL (2017) Folate-functionalized lipid nanoemulsion to deliver chemo-radiotherapeutics together for the effective treatment of nasopharyngeal carcinoma. AAPS PharmSciTech 18(4):1374–1381. doi:10.1208/s12249-016-0595-y

Liu LY, Jin Z, Wang M, Shen WY, Zhu ZZ, Wang Z, Liu LL (2018) W/O nano-emulsions with olive leaf phenolics improved oxidative stability of Sacha Inchi oil. Eur J Lipid Sci Technol 120(5):1700471. doi:10.1002/ejlt.201700471

Lucca LG, de Matos SP, de Mattos CB, Teixeira HF, Limberger RP, Veiga VF, de Araujo BV, Koester LS (2017) Nanoemulsification potentiates *in vivo* antiedematogenic effect of copaiba oil. J Biomed Nanotechnol 13(5):583−590. doi:10.1166/jbn.2017.2366

Lucca LG, de Matos SP, Kreutz T, Teixeira HF, Veiga VF, de Araujo BV, Limberger RP, Koester LS (2018) Anti-inflammatory effect from a hydrogel containing nanoemulsified copaiba oil (*Copaifera multijuga* Hayne). AAPS PharmSciTech 19(2):522−530. doi:10.1208/s12249-017-0862-6

Ma PH, Zeng QH, Tai KD, He XY, Yao YY, Hong XF, Yuan F (2017) Preparation of curcumin-loaded emulsion using high pressure homogenization: Impact of oil phase and concentration on physicochemical stability. LWT-Food Sci Techol 84:34–46. doi:10.1016/j.lwt.2017.04.074

Malhotra BD, Srivastava S, Ali MA, Singh C (2014) Nanomaterial-based biosensors for food toxin detection. Appl. Biochem. Biotechnol 174:880–896. doi:10.1007/s12010-014-0993-0

Marei GIK, Rabea EI, Badawy MEI (2018) Preparation and characterizations of chitosan/citral nanoemulsions and their antimicrobial activity. AFB 5(2):69–78. doi:10.22037/afb.v%vi%i.19005

Mate J, Periago PM, Palop A (2016) When nanoemulsified, D-limonene reduces *Listeria monocytogenes* heat resistance about one hundred times. Food Control 59:824–828. doi:10.1016/j.foodcont.2015.07.020

McClements DJ (2012) Nanoemulsions versus microemulsions: terminology, differences, and similarities. Soft Matter 8:1719–1729. doi: 10.1039/C2SM06903B

McClements DJ, Xiao H (2012) Potential biological fate of ingested nanoemulsions: influence of particle characteristics. Food Funct 3(3):202–220. doi:10.1039/c1fo10193e

McClements DJ (2013) Edible lipid nanoparticles: Digestion, absorption, and potential toxicity. Prog Lipid Res 52(4):409–423. doi:10.1016/j.plipres.2013.04.008

McClements DJ, Gumus CE (2016) Natural emulsifiers - Biosurfactants, phospholipids, biopolymers, and colloidal particles: Molecular and physicochemical basis of functional performance. Adv Colloid Interface Sci 234:3–26. doi:10.1016/j.cis.2016.03.002

Meghani N, Patel P, Kansara K, Ranjan S, Dasgupta N, Ramalingam C, Kumar A (2018) Formulation of vitamin D encapsulated cinnamon oil nanoemulsion: Its potential anti-

cancerous activity in human alveolar carcinoma cells. Colloids Surf B Biointerfaces 166:349–357. doi:10.1016/j.colsurfb.2018.03.041

Mendes C, Buttchevitz A, Kruger JH, Caon T, Benedet PO, Lemos-Senna EMT, Silva MAS (2017) Chitosan microencapsulation of the dispersed phase of an O/W nanoemulsion to hydrochlorothiazide delivery. J Microencapsul 34(7):611–622. doi:10.1080/02652048.2017.1373155

Meng LH, Xia XJ, Yang YF, Ye J, Dong WJ, Ma PP, Jin YQ, Liu YL (2016) Co-encapsulation of paclitaxel and baicalein in nanoemulsions to overcome multidrug resistance via oxidative stress augmentation and P-glycoprotein inhibition. Int J Pharm 513(1–2):8–16. doi:10.1016/j.ijpharm.2016.09.001

Migotto A, Carvalho VFM, Salata GC, da Silva FWM, Yan CYI, Ishida K, Costa-Lotufo LV, Steiner AA, Lopes LB (2018) Multifunctional nanoemulsions for intraductal delivery as a new platform for local treatment of breast cancer. Drug Deliv 25(1):654–667. doi:10.1080/10717544.2018.1440665

Mihindukulasuriya SDF, Lim LT (2014) Nanotechnology development in food packaging: A review. Trends Food Sci. Tech. 40:149–167. doi:10.1016/j.tifs.2014.09.009

Minz S, Pandey RS (2018) Development of adjuvanted solid fat nanoemulsions for pulmonary hepatitis B vaccination. J Pharm Sci 107(6):1701−1712. doi:10.1016/j.xphs.2018.02.007

Moghimi R, Aliahmadi A, Rafati H (2017) Ultrasonic nanoemulsification of food grade trans-cinnamaldehyde: 1,8-Cineol and investigation of the mechanism of antibacterial activity. Ultrason Sonochem 35:415–421. Part A. doi:10.1016/j.ultsonch.2016.10.020

Moghimipour E, Salimi A, Yousefvand T (2017) Preparation and evaluation of celecoxib nanoemulsion for ocular drug delivery. Asian J Pharm 11(3):S543−S550

Monge-Fuentes V, Muehlmann LA, Longo JPF, Silva JR, Fascineli ML, de Souza P, Faria F, Degterev IA, Rodriguez A, Carneiro FP, Lucci CM, Escobar P, Amorim RF, Azevedo RB (2017) Photodynamic therapy mediated by acai oil (*Euterpe oleracea* Martius) in nanoemulsion: A potential treatment for melanoma. J Photochem Photobiol B 166:301–310. doi:10.1016/j.jphotobiol.2016.12.002

Morsi N, Ibrahim M, Refai H, El Sorogy H (2017) Nanoemulsion-based electrolyte triggered in situ gel for ocular delivery of acetazolamide. Eur J Pharm Sci 104:302−314. doi:10.1016/j.ejps.2017.04.013

Mossa ATH, Abdelfatta NAH, Mohafrash SMM (2017) Nanoemulsion of camphor (*Eucalyptus globulus*) essential oil, formulation, characterization and insecticidal activity against wheat weevil, *Sitophilus granarius*. Asian Journal of Crop Science 9:50–62. doi: 10.3923/ajcs.2017.50.62

Mostafa DM, Abd El-Alim SH, Asfour MH, Al-Okbi SY, Mohamed DA, Awad G (2015a) Transdermal nanoemulsions of *Foeniculum vulgare* Mill. essential oil: Preparation, characterization and evaluation of antidiabetic potential. J Drug Deliv Sci Technol 29:99−106. doi:10.1016/j.jddst.2015.06.021

Mostafa DM, Kassem AA, Asfour MH, Al Okbi SY, Mohamed DA, Hamed TES (2015b) Transdermal cumin essential oil nanoemulsions with potent antioxidant and hepatoprotective activities: *In-vitro* and *in-vivo* evaluation. J Mol Liq 212:6−15. doi:10.1016/j.molliq.2015.08.047

Mungure TE, Roohinejad S, Bekhit AE, Greiner R, Mallikarjunan K (2018) Potential application of pectin for the stabilization of nanoemulsions. Curr Opin Food Sci 19:72–76. doi:10.1016/j.cofs.2018.01.011

Nam E, Yoo S, Kim HY, Kim YR, Heo YJ (2018) Transdermal water-in-oil nanocarriers of nitric oxide for triggering penile erection. Sci Rep 8:7312. doi:10.1038/s41598-018-25786-x

Nash JJ, Erk KA (2017) Stability and interfacial viscoelasticity of oil-water nanoemulsions stabilized by soy lecithin and Tween 20 for the encapsulation of bioactive carvacrol. Colloids Surf A Physicochem Eng Asp 517:1–11. doi:10.1016/j.colsurfa.2016.12.056

Nasr M, Nawaz S, Elhissi A (2012) Amphotericin B lipid nanoemulsion aerosols for targeting peripheral respiratory airways via nebulization. Int J Pharm 436(1−2):611−616. doi:10.1016/j.ijpharm.2012.07.028

Nastiti CMRR, Ponto T, Abd E, Grice JE, Benson HAE, Roberts MS (2017) Topical nano and microemulsions for skin delivery. Pharmaceutics 9(4):UNSP 37. doi:10.3390/pharmaceutics9040037

National Nanotechnology Initiative (2008) Nanotechnology: Big things from a tiny world. Arlington, VA

Naz Z, Ahmad FJ (2015) Curcumin-loaded colloidal carrier system: formulation optimization, mechanistic insight, *ex vivo* and *in vivo* evaluation. Int J Nanomedicine 10:4293−4307. doi:10.2147/IJN.S82788

Ni SL, Hu CB, Sun R, Zhao GD, Xia Q (2017) Nanoemulsions-based delivery systems for encapsulation of quercetin: Preparation, characterization, and cytotoxicity studies. J Food Process Eng 40(2):e12374. doi:10.1111/jfpe.12374

Oh YA, Oh YJ, Song AY, Won JS, Song KB, Min SC (2017) Comparison of effectiveness of edible coatings using emulsions containing lemongrass oil of different size droplets on grape berry safety and preservation. LWT Food Sci. Technol. 75:742–750

Ozogul Y, Durmus M, Ucar Y, Kosker AR, Ozogul F (2017) The combined impact of nanoemulsion based on commercial oils and vacuum packing on the fatty acid profiles of sea bass fillets. J Food Process Pres 41(6):e13222. doi:10.1111/jfpp.13222

Ozturk B, Argin S, Ozilgen M, McClements DJ (2014) Formation and stabilization of nanoemulsion-based vitamin E delivery systems using natural surfactants: Quillaja saponin and lecithin. J Food Eng 142:57−63. doi:10.1016/j.jfoodeng.2014.06.015

Ozturk B, Argin S, Ozilgen M, McClements DJ (2015) Nanoemulsion delivery systems for oil-soluble vitamins: Influence of carrier oil type on lipid digestion and vitamin D-3 bioaccessibility. Food Chem 187:499−506. doi:10.1016/j.foodchem.2015.04.065

Panatieri LF, Brazil NT, Faber K, Medeiros-Neves B, von Poser GL, Rott MB, Zorzi GK, Teixeira HF (2017) Nanoemulsions containing a coumarin-rich extract from *Pterocaulon balansae* (Asteraceae) for the treatment of ocular *Acanthamoeba keratitis*. AAPS PharmSciTech 18(3):721−728. doi:10.1208/s12249-016-0550-y

Pant M, Dubey S, Patanjali PK, Naik SN, Sharma S (2014) Insecticidal activity of eucalyptus oil nanoemulsion with karanja and jatropha aqueous filtrates. Int Biodeterior Biodegradation 91:119–127. doi: 10.1016/j.ibiod.2013.11.019

Parthasarathi S, Muthukumar SP, Anandharamakrishnan C (2016) The influence of droplet size on the stability, *in vivo* digestion, and oral bioavailability of vitamin E emulsions. Food Funct 7(5):2294–2302. doi:10.1039/c5fo01517k

Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MDP, Acosta-Torres LS, Diaz-Torres LA, Grillo R, Swamy MK, Sharma S, Habtemariam S, Shin HS (2018) Nano based drug delivery systems: recent developments and future prospects. J Nanobiotechnology 16(1):71. doi: 10.1186/s12951-018-0392-8

Pawar KR, Babu RJ (2014) Lipid materials for topical and transdermal delivery of nanoemulsions. Crit Rev Ther Drug Carrier Syst 31(5):429−458. doi:10.1615/CritRevTherDrugCarrierSyst.2014010663

Pellosi DS, Macaroff PP, Morais PC, Tedesco AC (2018) Magneto low-density nanoemulsion (MLDE): A potential vehicle for combined hyperthermia and photodynamic therapy to treat cancer selectively. Mater Sci Eng *C* Mater Biol Appl 92:103−111. doi:10.1016/j.msec.2018.06.033

Pentak D, Kozik V, Bak A, Dybal P, Sochanik A, Jampílek J (2016) Methotrexate and cytarabine – loaded nanocarriers for multidrug cancer therapy. Spectroscopic study. Molecules 21(12):1689. doi:10.3390/molecules21121689

Perazzo A, Preziosi V (2018) Catastrophic phase inversion techniques for nanoemulsification. Jafari SM, McClements DK (eds) Nanoemulsions Formulation, Applications, and

Characterization, AP Academic Press (Elsevier), London, pp 53−76. doi: https://doi.org/10.1016/B978-0-12-811838-2.00003-5
Pereira FG, Marquete R, Oliveira-Cruz L, Quintanilha-Falcao D, Mansur E, Moreira DD (2017) Cytotoxic effects of the essential oil from leaves of *Casearia sylvestris* Sw. (Salicaceae) and its nanoemulsion on A549 tumor cell line. B Latinoam Caribe Pl 16(5):506−512
Periasamy VS, Athinarayanan J, Alshatwi AA (2016) Anticancer activity of an ultrasonic nanoemulsion formulation of *Nigella sativa* L. essential oil on human breast cancer cells. Ultrason Sonochem 31:449–455. doi:10.1016/j.ultsonch.2016.01.035
Pinheiro AC, Coimbra MA,Vicente AA (2016) *In vitro* behaviour of curcumin nanoemulsions stabilized by biopolymer emulsifiers - Effect of interfacial composition. Food Hydrocoll 52:460–467. doi:10.1016/j.foodhyd.2015.07.025
Piorkowski DT, McClements DJ (2014) Beverage emulsions: Recent developments in formulation, production, and applications. Food Hydrocoll 42:5–41. Part: 1. doi:10.1016/j.foodhyd.2013.07.009
Pisarčík M, Lukáč M, Jampílek J, Bilka F, Bilková A, Pašková Ľ, Devínsky F, Horáková R, Opravil T (2018) Silver nanoparticles stabilised with cationic single-chain surfactants. Structure-physical properties-biological activity relationship study. J Mol Liq 272:60-72. doi:10.1016/j.molliq.2018.09.042
Prakash B, Kujur A, Yadav A, Kumar A, Singh PP, Dubey NK (2018a) Nanoencapsulation: An efficient technology to boost the antimicrobial potential of plant essential oils in food system. Food Control 89: 1–11. doi:10.1016/j.foodcont.2018.01.018
Prakash A, Baskaran R, Paramasivam N, Vadivel V (2018b) Essential oil based nanoemulsions to improve the microbial quality of minimally processed fruits and vegetables: A review. Food Res Int 111:509–523. doi:10.1016/j.foodres.2018.05.066
Prasad R, Kumar V, Prasad KS (2014) Nanotechnology in sustainable agriculture: present concerns and future aspects. Afr J Biotechnol 13(6): 705-713
Prasad R, Pandey R, Barman I (2016) Engineering tailored nanoparticles with microbes: quo vadis. WIREs Nanomed Nanobiotechnol 8:316–330. doi: 10.1002/wnan.1363
Prasad R, Bhattacharyya A, Nguyen QD (2017a) Nanotechnology in sustainable agriculture: Recent developments, challenges, and perspectives. Front Microbiol 8:1014. doi:10.3389/fmicb.2017.01014
Prasad R, Pandey R, Varma A, Barman I (2017b) Polymer based nanoparticles for drug delivery systems and cancer therapeutics. In: Natural Polymers for Drug Delivery (eds. Kharkwal H and Janaswamy S), CAB International, UK 53-70
Prasad M, Lambe UP, Brar B, Shah I, J Manimegalai J, Ranjan K, Rao R, Kumar S, Mahant S, Khurana SK, Iqbal HMN, Dhama K, Misri J, Prasad G (2018) Nanotherapeutics: An insight into healthcare and multi-dimensional applications in medical sector of the modern world. Biomed Pharmacother 97:1521–1537. doi: 10.1016/j.biopha.2017.11.026
Primozic M, Duchek A, Nickerson M, Ghosh S (2018) Formation, stability and *in vitro* digestibility of nanoemulsions stabilized by high-pressure homogenized lentil proteins isolate. Food Hydrocoll 77:126–141. doi:10.1016/j.foodhyd.2017.09.028
Prow TW, Grice JE, Lin LL, Faye R, Butler M, Becker W, Wurm EMT, Yoong C, Robertson TA, Soyer HP, Roberts MS (2011) Nanoparticles and microparticles for skin drug delivery. Adv Drug Deliv Rev 63(6):470−491. doi:10.1016/j.addr.2011.01.012
Qadir A, Faiyazuddin MD, Hussain MDT, Alshammari TM, Shakeel F (2016) Critical steps and energetics involved in a successful development of a stable nanoemulsion. J Mol Liq 214:7-18. doi:10.1016/j.molliq.2015.11.050
Qian C, McClements DJ (2011) Formation of nanoemulsions stabilized by model food-grade emulsifiers using high-pressure homogenization: Factors affecting particle size. Food Hydrocoll 25(5):1000–1008. doi:10.1016/j.foodhyd.2010.09.017
Rachmawati H, Budiputra DK, Mauludin R (2015) Curcumin nanoemulsion for transdermal application: formulation and evaluation. Drug Dev Ind Pharm 41(4):560−566. doi:10.3109/03639045.2014.884127

Radi M, Akhavan-Darabi S, Akhavan, HR, Amiri S (2018) The use of orange peel essential oil microemulsion and nanoemulsion in pectin-based coating to extend the shelf life of fresh-cut orange. J Food Process Preserv 42(2):e13441. doi:10.1111/jfpp.13441

Rai VK, Mishra N, Yadav KS, Yadav NP (2018) Formulation development, stability issues, basic considerations and applications. J Control Release 270:203−225. doi:10.1016/j.jconrel.2017.11.049

Raliya R, Saharan V, Dimpka C, Biswas P (2018) Nanofertilizer for precision and sustainable agriculture: Current state and future perspectives. J Agric Food Chem 66(26):6487−6503. doi:10.1021/acs.jafc.7b02178

Raviadaran R, Chandran D, Shin LH, Manickam S (2018) Optimization of palm oil in water nano-emulsion with curcumin using microfluidizer and response surface methodology. LWT-Food Sci Technol 96:58−65. doi:10.1016/j.lwt.2018.05.022

Rodriguez J, Martin MJ, Ruiz MA, Clares B (2016) Current encapsulation strategies for bioactive oils: From alimentary to pharmaceutical perspectives. Food Res Int 83:41−59. doi:10.1016/j.foodres.2016.01.032

Rosa MTMG, Silva EK, Santos DT, Petenate AJ, Meireles MAA (2016) Obtaining annatto seed oil miniemulsions by ultrasonication using aqueous extract from Brazilian ginseng roots as a biosurfactant. J Food Eng 168:68−78. doi:10.1016/j.jfoodeng.2015.07.024

Roy A, Guha P (2018) Formulation and characterization of betel leaf (*Piper betle* L.) essential oil based nanoemulsion and its *in vitro* antibacterial efficacy against selected food pathogens. J Food Process Preserv 42(6):e13617. doi:10.1111/jfpp.13617

Sabry AH, Ragaei M (2018) Nanotechnology and their applications in insect's pest control. In: Abd-Elsalam KA, Prasad R (eds) Nanobiotechnology Applications in Plant

Protection, Nanotechnology in the Life Sciences, Springer International Publishing AG, part of Springer Nature, Cham, Switzerland, pp 1–28. https://doi.org/10.1007/978-3-319-91161-8_1

Sahu P, Das D, Mishra VK, Kashaw V, Kashaw SK (2017) Nanoemulsion: A novel eon in cancer chemotherapy. Mini Rev Med Chem 17(18):1778−1792. doi:10.2174/1389557516666160219122755

Salim N, Ahmad N, Musa SH, Hashim R, Tadros TF, Basri M (2016) Nanoemulsion as a topical delivery system of antipsoriatic drugs. RSC Adv 6(8):6234−6250. doi:10.1039/c5ra14946k

Salvia-Trujillo L, Rojas-Graue MA, Soliva-Fortuny R, Martin-Belloso O (2014) Impact of microfluidization or ultrasound processing on the antimicrobial activity against *Escherichia coli* of lemongrass oil-loaded nanoemulsions. Food Control 37:292−297. doi:10.1016/j.foodcont.2013.09.015

Salvia-Trujillo L, Rojas-Graue A, Soliva-Fortuny R, Martin-Belloso O (2015) Physicochemical characterization and antimicrobial activity of food-grade emulsions and nanoemulsions incorporating essential oils. Food Hydrocoll 43:547−556. doi:10.1016/j.foodhyd.2014.07.012

Sanchez-Ortega I, Garcia-Almendarez BE, Santos-Lopez EM, Reyes-Gonzalez, LR, Regalado C (2016) Characterization and antimicrobial effect of starch-based edible coating suspensions. Food Hydrocoll 52:906−913. doi:10.1016/j.foodhyd.2015.09.004

Sandig AG, Campmany ACC, Campos FF, Villena MJM, Naveros BC (2013) Transdermal delivery of imipramine and doxepin from newly oil-in-water nanoemulsions for an analgesic and anti-allodynic activity: Development, characterization and *in vivo* evaluation. Colloids Surf B Biointerfaces 103:558−565. doi:10.1016/j.colsurfb.2012.10.061

Sasikumar A, Kamalasanan K (2017) Nanomedicine for prostate cancer using nanoemulsion: A review. J Control Release 260:111−123. doi:10.1016/j.jconrel.2017.06.001

Saxena V, Hasan A, Sharma S, Pandey LM (2018) Edible oil nanoemulsion: An organic nanoantibiotic as a potential biomolecule delivery vehicle. Int J Polym Mater Po 67(7):410–419. doi:10.1080/00914037.2017.1332625

Sekhon BS (2014) Nanotechnology in agri-food production: an overview. Nanotechnol Sci Appl 7:31–53. doi:10.2147/NSA.S39406

Sengupta P, Chatterjee B (2017) Potential and future scope of nanoemulgel formulation for topical delivery of lipophilic drugs. Int J Pharm 526(1−2):353−365. doi:10.1016/j.ijpharm.2017.04.068

Sessa M, Ferrari G, Donsi F (2015) Novel edible coating containing essential oil nanoemulsions to prolong the shelf life of vegetable products. In: Pierucc S, Klemes JJ (ed) ICHEAP12: 12th International Conference on Chemical & Process, Engineering Book Series: Chemical Engineering Transactions 43:55–60. doi:10.3303/CET1543010

Severino R, Vu KD, Donsi F, Salmieri S, Ferrari G, Lacroix M (2014) Antibacterial and physical effects of modified chitosan based-coating containing nanoemulsion of mandarin essential oil and three non-thermal treatments against *Listeria innocua* in green beans. Int J Food Microbiol 191:82–88. doi:10.1016/j.ijfoodmicro.2014.09.007

Severino R, Ferrari G, Vu KD, Donsi F, Salmieri S, Lacroix M (2015) Antimicrobial effects of modified chitosan based coating containing nanoemulsion of essential oils, modified atmosphere packaging and gamma irradiation against *Escherichia coli* O157:H7 and *Salmonella Typhimurium* on green beans. Food Control 50:215–222. doi:10.1016/j.foodcont.2014.08.029

Shah K, Chan LW, Wong TW (2017) Critical physicochemical and biological attributes of nanoemulsions for pulmonary delivery of rifampicin by nebulization technique in tuberculosis treatment. Drug Deliv 24(1):1631−1647. doi:10.1080/10717544.2017.1384298

Shahabi N, Tajik H, Moradi M, Forough M, Ezati P (2017) Physical, antimicrobial and antibiofilm properties of *Zataria multiflora* Boiss essential oil nanoemulsion. Int J Food Sci Technol 52(7):1645−1652. doi:10.1111/ijfs.13438

Shakeel F, Ramadan W, Faisal MS, Rizwan M, Faiyazuddin M, Mustafa G, Shafiq S (2010) Transdermal and topical delivery of anti-inflammatory agents using nanoemulsion/microemulsion: An updated review. Curr Nanosci 6(2):184−198. doi:10.2174/157341310790945740

Shao P, Qiu Q, Xiao J, Zhu YG, Sun PL (2017) Chemical Stability and *in vitro* release properties of β-carotene in emulsions stabilized by *Ulva fasciata* polysacharide. Int J Biol Macromol 102:225–231. doi:10.1016/j.ijbiomac.2017.03.186

Shao Y, Wu CH, Wu TT, Li Y, Chen SG, Yuan CH, Hu YQ (2018) Eugenol-chitosan nanoemulsions by ultrasound-mediated emulsification: Formulation, characterization and antimicrobial activity. Carbohydr Polym 193:144–152. doi:10.1016/j.carbpol.2018.03.101

Sharif HR, Abbas S, Majeed H, Safdar W, Shamoon M, Khan MA, Shoaib M, Raza H, Haider J (2017a) Formulation, characterization and antimicrobial properties of black cumin essential oil nanoemulsions stabilized by OSA starch. J Food Sci Tech Mys 54(10):3358–3365. doi:10.1007/s13197-017-2800-8

Sharif HR, Goff HD, Majeed H, Liu F, Nsor-Atindana J, Haider J, Liang R, Zhong F (2017b) Physicochemical stability of β-carotene and α-tocopherol enriched nanoemulsions: Influence of carrier oil, emulsifier and antioxidant. Colloids Surf A Physicochem Eng Asp 529:550–559. doi:10.1016/j.colsurfa.2017.05.076

Sharma M, Mann B, Sharma R, Bajaj R, Athira S, Sarkar P, Pothuraju R (2017) Sodium caseinate stabilized clove oil nanoemulsion: Physicochemical properties. J Food Eng 212:38–46. doi:10.1016/j.jfoodeng.2017.05.006

Sharma A, Sharma NK, Srivastava A, Kataria A, Dubey S, Sharma S, Kundu B (2018) Clove and lemongrass oil based non-ionic nanoemulsion for suppressing the growth of plant

pathogenic *Fusarium oxysporum* f.sp. *lycopersici*. Ind Crops Products 123:353–362. doi: 10.1016/j.indcrop.2018.06.077

Shen J, Liu XD, Zhou M, Liu HJ (2018) Novel nanoemulsion formulation for ocular drug delivery for cataract therapeutics. JBT 8(5):647−657. doi:10.1166/jbt.2018.1790

Shi J, Zhou SL, Kang L, Ling H, Chen JP, Duan LL, Song YZ, Deng YH (2018) Evaluation of the antitumor effects of vitamin K-2 (menaquinone-7) nanoemulsions modified with sialic acid-cholesterol conjugate. Drug Deliv Transl Res 8(1):1−11. doi:10.1007/s13346-017-0424-1

Shinde RL, Devarajan PV (2017) Docosahexaenoic acid-mediated, targeted and sustained brain delivery of curcumin microemulsion. Drug Deliv 24(1):152−161. doi:10.1080/10717544.2016.1233593

Shofia SI, Jayakumar K, Mukherjee A, Chandrasekaran N (2018) Efficiency of brown seaweed (*Sargassum longifolium*) polysaccharides encapsulated in nanoemulsion and nanostructured lipid carrier against colon cancer cell lines HCT 116. RSC Adv 8(29):15973−15984. doi:10.1039/c8ra02616e

Shu GF, Khalid N, Tan TB, Zhao YG, Neves MA, Kobayashi I, Nakajima M (2018) *In vitro* bioaccessibility of ergocalciferol in nanoemulsion-based delivery system: the influence of food-grade emulsifiers with different stabilising mechanisms. Int J Food Sci Technol 53(2):430–440. doi:10.1111/ijfs.13601

Silva LFC, Lemos-Senna E (2016) Development of triamcinolone acetonide-loaded nanoemulsion for ophthalmic drug delivery. Lat Am J Pharm 35(10):2159−2168

Singh OV (2015) Bio-nanoparticles: Biosynthesis and sustainable biotechnological implications. Wiley-Blackwell, Hoboken

Singh T, Shukla S, Kumar P, Wahla V, Bajpai VK, Rather IA (2017a) Application of nanotechnology in food science: Perception and overview. Front Microbiol 8:1501. doi: 10.3389/fmicb.2017.01501

Singh, Y, Meher JG, Raval K, Khan FA, Chaurasia M, Jain NK, Chourasia MK (2017b) Nanoemulsion: Concepts, development and applications in drug delivery. J Control Release 252:28–49. doi:10.1016/j.jconrel.2017.03.008

Slomkowski S, Alemán JV, Gilbert RG, Hess M, Horie K, Jones RG, Kubisa P, Meisel I, Mormann W, Penczek S, Stepto RFT (2011) Terminology of polymers and polymerization processes in dispersed systems (IUPAC Recommendations 2011). Pure Appl Chem 83:2229–2259. doi:10.1351/PAC-REC-10-06-03

Souza JG, Dias K, Pereira TA, Bernardi DS, Lopez RFV (2014) Topical delivery of ocular therapeutics: carrier systems and physical methods. J Pharm Pharmacol 66(4):507−530. doi:10.1111/jphp.12132

Steuber N, Vo K, Wadhwa R, Birch J, Iacoban P, Chavez P, Elbayoumi TA (2016) Tocotrienol nanoemulsion platform of curcumin elicit elevated apoptosis and augmentation of anticancer efficacy against breast and ovarian carcinomas. Int J Mol Sci 17(11):1792. doi:10.3390/ijms17111792

Su R, Fan WF, Yu Q, Dong XC, Qi JP, Zhu QG, Zhao WL, Wu W, Chen ZJ, Li Y, Lu Y (2017) Size-dependent penetration of nanoemulsions into epidermis and hair follicles: implications for transdermal delivery and immunization. Oncotarget 8(24):38214−38226. doi:10.18632/oncotarget.17130

Sugumar S, Ghosh V, Nirmala MJ, Mukherjee A, Chandrasekaran N (2014) Ultrasonic emulsification of eucalyptus oil nanoemulsion: Antibacterial activity against *Staphylococcus aureus* and wound healing activity in Wistar rats. Ultrason Sonochem 21(3):1044−1049. doi:10.1016/j.ultsonch.2013.10.021

Taghavi E, Mirhosseini H, Rukayadi Y, Radu S, Biabanikhankahdani R (2018) Effect of microfluidization condition on physicochemical properties and inhibitory activity of nanoemulsion loaded with natural antibacterial mixture. Food Bioprocess Technol 11(3):645–659. doi:10.1007/s11947-017-2037-6

Tayeb HH, Sainsbury F (2018) Nanoemulsions in drug delivery: formulation to medical application. Nanomedicine, in press. doi: 10.2217/nnm-2018-0088.

Tayel SA, El-Nabarawi MA, Tadros MI, Abd-Elsalam WH (2013) Design, *in vitro* characterization and *in vivo* estimation of the ocular irritation and drug pharmacokinetics in the aqueous humor of rabbits. Int J Pharm 443(1−2):293−305. doi:10.1016/j.ijpharm.2012.12.049

Teng J, Hu XQ, Wang MF, Tao NP (2018) Fabrication of chia (*Salvia hispanica* L.) seed oil nanoemulsions using different emulsifiers. J Food Process Preserv 42(1):e13416. doi:10.1111/jfpp.13416

Tian HX, Li DF, Xu T, Hu J, Rong YZ, Zhao B (2017) Citral stabilization and characterization of nanoemulsions stabilized by a mixture of gelatin and Tween 20 in an acidic system. J Sci Food Agric 97(9):2991–2998. doi:10.1002/jsfa.8139

Topuz OK, Ozvural EB, Zhao Q, Huang QR, Chikindas M, Golukcu M (2016) Physical and antimicrobial properties of anise oil loaded nanoemulsions on the survival of foodborne pathogens. Food Chem 203:117−123. doi:10.1016/j.foodchem.2016.02.051

Uluata S, McClements DJ, Decker EA (2015) Physical stability, autoxidation, and photosensitized oxidation of ω-3 oils in nanoemulsions prepared with natural and synthetic surfactants. J Agric Food Chem 63(42):9333–9340. doi:10.1021/acs.jafc.5b03572

van Straten D, Mashayekhi V, de Bruijn HS, Oliveira S, Robinson DJ (2017) Oncologic photodynamic therapy: Basic principles, current clinical status and future directions. Cancers 9(2):19. doi:10.3390/cancers9020019

Vecchione R, Quagliariello V, Calabria D, Calcagno V, De Luca E, Iaffaioli RV, Netti PA (2016) Curcumin bioavailability from oil in water nano-emulsions: *In vitro* and *in vivo* study on the dimensional, compositional and interactional dependence. J Control Release 233:88−100. doi:10.1016/j.jconrel.2016.05.004

Ventola CL (2017) Progress in nanomedicine: Approved and investigational nanodrugs. P T 42(12):742–755

Verma P, Meher JG, Asthana S, Pawar VK, Chaurasia M, Chourasia MK (2016) Perspectives of nanoemulsion assisted oral delivery of docetaxel for improved chemotherapy of cancer. Drug Deliv 23(2):479–488. doi:10.3109/10717544.2014.920430

Walia N, Dasgupta N, Ranjan S, Chen LY, Ramalingam C (2017) Fish oil based vitamin D nanoencapsulation by ultrasonication and bioaccessibility analysis in simulated gastro-intestinal tract. Ultrason Sonochem 39:623−635. doi:10.1016/j.ultsonch.2017.05.021

Walker RM, Gumus CE, Decker EA, McClements DJ (2017) Improvements in the formation and stability of fish oil-in-water nanoemulsions using carrier oils: MCT, thyme oil, & lemon oil. J Food Eng 211:60−68. doi:10.1016/j.jfoodeng.2017.05.004

Wang L, Li X, Zhang G, Dong JF, Eastoe J (2007) Oil-in-water nanoemulsions for pesticide formulations. J Colloid Interface Sci 314:230–235. doi: 10.1016/j.jcis.2007.04.079

Wang C, Tai X, Du Z, Liu X (2017) Formulation and physicochemical properties of promising avermectin microemulsion with biodegradable surfactant and oil. J Disper Sci and Technol 38:409–415. doi: 10.1080/01932691.2016.1172315

Wu CH, Wang LP, Hu YQ, Chen, SG, Liu DH, Ye XQ (2016) Edible coating from citrus essential oil-loaded nanoemulsions: physicochemical characterization and preservation performance. RSC Adv 6(25):20892–20900. doi:10.1039/c6ra00757k

Xu F, Pandya JK, Chung C, McClements DJ, Kinchla A (2018) Emulsions as delivery systems for gamma and delta tocotrienols: Formation, properties and simulated gastrointestinal fate. Food Res Int 105:570–579. doi:10.1016/j.foodres.2017.11.033

Yalcinoz S, Ercelebi E (2018) Potential applications of nano-emulsions in the food systems: an update. Mater Res Express 5(6):062001. doi:10.1088/2053-1591/aac7ee

Yan B, Park SH, Balasubramaniam VM (2017) Influence of high pressure homogenization with and without lecithin on particle size and physicochemical properties of whey protein-based emulsions. J Food Process Eng 40(6):UNSP e12578. doi:10.1111/jfpe.12578

Yang Y, Leser ME, Sher AA, McClements DJ (2013) Formation and stability of emulsions using a natural small molecule surfactant: Quillaja saponin (Q-Naturale®). Food Hydrocoll 30(2):589–596. doi:10.1016/j.foodhyd.2012.08.008

Yang C, Powell CA, Duan Y, Shatters, Zhang M (2015) Antimicrobial nanoemulsion formulation with improved penetration of foliar spray through citrus leaf cuticles to control citrus huanglongbing. PLoS ONE 10(7):e0133826. doi: 10.1371/journal.pone.0133826

Yang CC, Hung CF, Chen BH (2017) Preparation of coffee oil-algae oil-based nanoemulsions and the study of their inhibition effect on UVA-induced skin damage in mice and melanoma cell growth. Int J Nanomedicine 12:6559−6580. doi:10.2147/IJN.S144705

Yerramilli M, Longmore N, Ghosh S (2017) Improved stabilization of nanoemulsions by partial replacement of sodium caseinate with pea protein isolate. Food Hydrocoll 64:99–111. doi:10.1016/j.foodhyd.2016.10.027

Yu WY, Zhang N (2009) Surface modification of nanocarriers for cancer therapy. Curr Nanosci 5(2):123–134. doi:10.2174/157341309788185370

Yukuyama MN, Kato ETM, Loebenberg R, Bou-Chacra NA (2017) Challenges and future prospects of nanoemulsion as a drug delivery system. Curr Pharm Des 23(3):495−508. doi:10.2174/1381612822666161027111957

Zambrano-Zaragoza ML, Gutierrez-Cortez E, Del Real A, Gonzalez-Reza RM, Galindo-Perez MJ, Quintanar-Guerrero D (2014) Fresh-cut Red Delicious apples coating using tocopherol/mucilage nanoemulsion: Effect of coating on polyphenol oxidase and pectin methylesterase activities. Food Res Int 62:974–983. doi:10.1016/j.foodres.2014.05.011

Zhang SJ, Zhang M, Fang ZX, Liu YP (2017) Preparation and characterization of blended cloves/cinnamon essential oil nanoemulsions. LWT-Food Sci Technol 75:316–322. doi:10.1016/j.lwt.2016.08.046

Zhang Y, Pan K, Zhong QX (2018) Eugenol nanoencapsulated by sodium caseinate: Physical, antimicrobial, and biophysical properties. Food Biophys 13(1):37–48. doi:10.1007/s11483-017-9509-0

Zhao XJ, Zhou ZQ (2016) Synthesis and applications of pectin-based nanomaterials. Curr Nanosci 12(1):103–109. doi:10.2174/1573413711666150818224020

Zhao X, Zhu Y, Zhang C, Kei JM, Yu M, Du FP (2017) Positive charge pesticide nanoemulsions prepared by the phase inversion composition method with ionic liquids. RSC Adv 7:48586–48596. doi: 10.1039/C7RA08653A

Zhao CH, Shen X, Guo MR (2018a) Stability of lutein encapsulated whey protein nano-emulsion during storage. PLoS ONE 13(2):e0192511. doi:10.1371/journal.pone.0192511

Zhao J, Liu S, Hu XY, Zhang YM, Yan SL, Zhao H, Zeng M, Li Y, Yang L, Zhang JQ (2018b) Improved delivery of natural alkaloids into lung cancer through woody oil-based emulsive nanosystems Drug Deliv 25(1):1426–1437. doi:10.1080/10717544.2018.1474970