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REVIEW PAPER

A review of topical micro- and nanoemulsions for common skin diseases

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ABSTRACT

Microemulsions (MEs) and nanoemulsions (NEs) are dispersions of two immiscible liquids which are usually transparent/translucent. Several reports are available on uses of MEs/NEs to increase efficacy of the loaded active ingredient(s) in topical dosage forms. This review aims to describe brief applications of MEs/NEs in common skin diseases as well as skincare products. Advantages of MEs/NEs in comparison with the traditional bulk form, including their improved efficacy and safety, have been discussed to highlight the importance of use of such delivery systems. The review briefs mechanism of action of MEs/NEs in enhancing delivery of the cargo. Furthermore, applications of MEs/NEs in common skin diseases including infectious rashes, pigmentation disorders (hyperpigmentaion and hypopigmentation), wound healing, skin cancers and scaling patches and plaques/papulosquamous disorders (psoriasis, atopic dermatitis and acne) have been discussed. MEs/NEs in skin care products have also been reviewed here.

Keywords: *Infections, Microemulsion, Nanoemulsion, Skin, Skin care, Skin disease, Topical*

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INTRODUCTION

Emulsions are dispersions of two immiscible liquids. To be stabilized, they require a third component, namely, surfactant. The surfactant plays a major role in determining the type of the emulsion: oil-in-water (O/W) emulsions require a water-soluble surfactant while oil-soluble surfactants contribute to the formation of water-in-oil (W/O) emulsions [1, 2]. Surfactants reduce interfacial tension and stabilize the emulsions. In an emulsion system, the surfactant molecules form a layer between the oil and the water molecules. In pharmaceutical applications, the most widely used surfactants are polyoxyethylene sorbitan monolaurate (Tweens) and sorbitan monolaurate (Spans). Other surfactants such as bile salts, Pluronics, SDS (sodium dodecyl sulfate),

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lecithin and sodium deoxycholate are also being regularly observed in the literature. To find the right surfactant for emulsifying a specific oil, hydrophilic–lipophilic balance (HLB) is commonly applied. HLB which indicates the size of the hydrophilic part(s) of a surfactant molecule, is close to 0 when the surfactant is lipophilic and close to 20 when the surfactant is hydrophilic. In general, HLB value of 8-18 is used for formation of oil in water emulsions, while formation of water in oil emulsions requires HLB value of 3-6 [3].

Looking at the existing literature, there is no distinctive definition between microemulsion (ME) and nanoemulsion (NE) systems. While some papers have tried to use stability profile of the emulsions for naming an emulsion system as ME or NE, some more recent ones have used their particle size to distinguish a NE from a ME: Before introduction of the term "nanotechnology" or when nanotechnology was just in its early stages, all thermodynamically stable dispersions which were single optically isotropic had been named as MEs (even if the particle size was in nanometer range) [4]. At that time, the term NE was sometimes used for the emulsions indicated kinetic stability [5]. This definition is still being used frequently [6]. However, in recent decades, with increasing attentions to "nano", NEs are being defined in a new way: emulsions with particle size in the nanometer range, regardless of their stability profile are called NEs [7]. Reviewing the literature, several upper and/or lower limits have been mentioned for size of NE particles. They include 20-200 nm [8], 100-600 nm [9], <200 nm [10], <500 nm [11] and <100 nm [12]. Interestingly, at the same time, particle size of <100 nm has been used for MEs, irrespective of its stability profile [13]. In this paper, to prevent missing the reports, all colloidal emulsions with particle size less than around 1 µm have been reviewed and no judgement has been made about the naming system that the authors have used in the original papers.

MEs/NEs have been used in various dosage forms. Examples include topical gel [14, 15], topical cream [16] aerosol [17, 18] to be used intravenous [19], intramuscular [20], oral [21] and intranasal [22]. The main advantages of MEs/NEs in drug delivery systems include ease of preparation, optical clarity [4], increased drug bioavailability, decreased toxicity profile as well as taste masking capability. They are also able to solubilize lipophilic molecules in aqueous media [23, 24].

To prepare MEs/NEs, usually an energy input is required. MEs/NEs are prepared by high or low energy methods. In general, low energy methods include phase inversion (by either tailoring concentration of surfactant and co-surfactant or changing the temperature to induce self-assembly) and spontaneous emulsification (combining oil, water, and surfactant(s) above a critical concentration for formation of emulsion). High energy methods include ultrasonication (high-frequency sound waves that disrupt oil and water phases), high-pressure homogenization (forcing the mixture through a narrow orifice under high pressure) and microfluidization (precisely controlled microchannels that are used to prepare the emulsion) (Fig. 1) [3, 25].

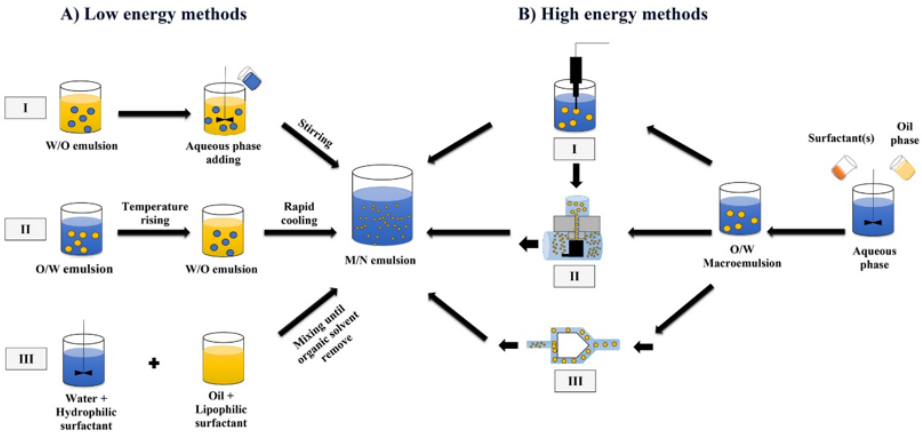

Fig. 1. Common methods for preparation of micro- and nano-emulsions. A. Low-Energy Methods: I. Phase Inversion Composition: tailoring surfactant and co-surfactant ratios to induce spontaneous emulsification. II. Phase Inversion Temperature: heating or cooling a mixture across a specific temperature to trigger self-assembly. III. Spontaneous Emulsification: combining oil, water, and surfactant(s) above a critical concentration, leading to emulsion formation. B. High-Energy Methods: I. Ultrasonication: high-frequency sound waves, disrupting oil and water phases, creating nano-sized particles. II. High-Pressure Homogenization: forcing the mixture through a narrow orifice under high pressure. III. Microfluidization: microchannels that control particle size and distribution through laminar flow.

Mechanism of action

It is now generally accepted that MEs/NEs are able to improve absorption/bioavailability of active ingredients through different administration routes [26]. For instance, in our previous report, oral bioavailability of atovaquone, a suppressor of protozoan parasites, increased significantly when given in NE form, compared with that of bulk form (i.e. area under the curve ($AUC_{0-\infty}$) 13,722 (µg/ml) in NE containing atovaquone vs. 2,193 (µg/ml) in suspension of atovaquone) [27]. Also, when administered topically, NEs appear not to affect the systemic absorption of the cargo [28, 29]. Several mechanisms have been suggested for this increase. They include:

- increasing the solubility of the hydrophobic drugs [30]
- the small particle size that makes increased transport [31] and fast release into the aqueous medium [32]
- Enhanced interaction of the particles with their targets, including membranes, as a function of smaller particle size [33]
- Effect of lipid vehicles in slowing down the gastric emptying and forming lipoproteins (to improve the transport of hydrophobic drugs) [34]
- Presence of surfactants that help the drug spread better though the lumen [34], enhance epithelial permeability [35] and interact faster with skin lipids [36].
- Existence of water as a powerful penetration enhancer [37].
- Ability of NE components to disrupt the integrity of stratum corneum (SC) [38].

Topical delivery of micro and nanoemulsions

Topical delivery of drugs, although is an interesting approach, has remained to be a challenge for formulators due to the presence of SC. The majority of active ingredients, when applied topically, are not able to penetrate the SC, thus, continuous researches are being performed to discover novel and safe penetration enhancers [39]. So far, several formulations of bioactive agents have been prepared by encapsulating them into various nanocarriers such as MEs, NEs, liposomes, niosomes, solid lipid nanoparticles (SLNs), nanocapsules and dendrimers [40]. Among them, MEs and NEs are highly attractive for topical delivery purposes. They have advantages such as low skin irritation, high drug loading capacity and ability to hydrate the skin [41, 42] as well as proper spreadability and penetration through the skin [43, 44]. Interestingly, they have also shown the potential to help peptides (e.g. bee venom) penetrate through the skin [45, 46].

When used topically, the concentration of ingredients plays a crucial role in enhancing the skin permeability of MEs/NEs [47]. The most important factor is the surfactant. Surfactants bind to keratin filaments, distort corneocytes and alter the SC permeability [48]. In a study, a ME containing a lipophilic (progesterone) and a hydrophilic (adenosine) drugs enhanced flux of both drugs while increasing the surfactant concentration managed to double the transdermal flux of adenosine only [49]. Details of the safety issues of MEs/NEs and in particular the concerns related to the use of surfactants have been discussed previously [3]. Co-surfactants are also important in increasing the solubility of the ingredients [50]. Furthermore, they help dispersion of the surfactants in the oil phase and increase the formulation's homogeneity and stability [51]. Co-surfactants affect the viscosity and release profile of the MEs/NEs. Choosing the right co-surfactant can improve the overall flux of the drug without the need for another penetration enhancer [38].

Reviewing the literature, limited review articles are available that have partly or wholly discussed application of MEs/NEs in skin diseases (Fig. 2). For instance, Ramanunny et al. have reviewed different colloidal nanocarriers for some dermatological diseases [52]. Topical uses of MEs were also reviewed in 2011, focusing on their properties as antifungal, antimicrobial

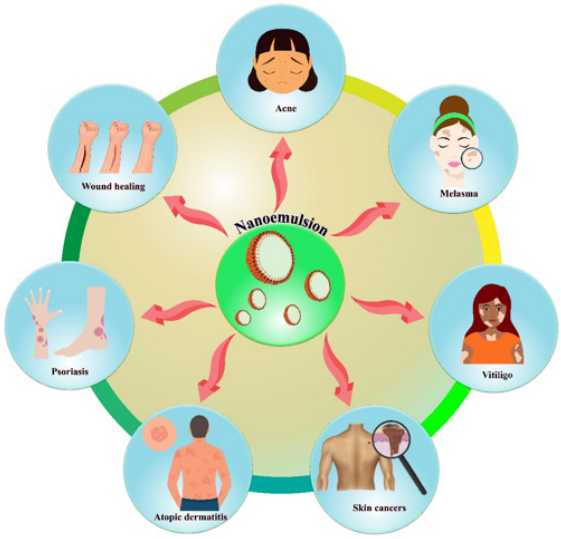

Fig. 2. An overview of the application of MEs/NEs in skin diseases

and antioxidant properties [53]. To the best of our knowledge, no recent review is available on applications of MEs/NEs in common skin diseases, which is the aim of our review.

Infectious rashes

Skin surface infections are observed in most people at least once in their lives. Most skin infections are painless and do not need any treatment. However, they may affect skin's beauty and destroy its integrity as the first defense line of the innate immune system [54]. Infectious rashes, as a widespread skin disease, are caused by bacteria, viruses and fungus. In some cases, they need to be treated by suitable delivery systems of potent medications [55]. (Table 1).

It is now well-known that bioavailability is a major obstacle in many delivery systems. In several investigations to overcome the limitations of oral and topical medicines, ME/NE-based formulations have been developed to treat bacterial rashes [56]. For example, Seema et al. increased the delivery of mupirocin using NEs [57]. In another report, a rifampicin-loaded NE showed intense antibacterial activity against *Staphylococcus aureus* [58]. Furthermore, NE containing penicillin G showed appreciable stability (4 months at 4 °C), with proper antibacterial activity, compared to free penicillin G [59]. A cinnamon oil NE indicated improved antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* [60].

It is believed that NEs make antibiotics more effective by altering the membrane integrity of the bacteria [61]. For instance, NEs with positive charge attach electrostatically to the negatively charged membranes of bacteria. By enhancing the local concentration of the drug and enhancing its permeability, increased performance is expected [59]. A cationic NE, loaded by fusidic acid (size 20-110 nm), managed to eradicate methicillin-resistant *Staphylococcus aureus*. *Ex-vivo* and *in-vivo* results showed that the NE increased skin permeability of fusidic acid and improved epithelialization of the damaged skin [62].

Considering the limitations of conventional antibiotics, such as drug resistance, the effects of NEs having antibacterial agents have been studied on different bacteria. A NE containing linoleic acid showed an acceptable bactericidal effect on *Staphylococcus aureus.* The NE had mean particle size of about 75 nm which was stable for 3 months at 4 °C. The study illustrated that formulation of linoleic acid into the nano-form significantly increased its antibacterial effect (up to 250 folds) [63]. Another NE containing 6% V/V *Cleome viscosa* essential oil (mean particle size 7 nm) showed extensive antibacterial effect on drug-resistant bacteria, including *Staphylococcus aureus* and *Streptococcus pyogenes* [64]. Sugumar et al. prepared a NE containing Eucalyptus oil (mean particle size 3.8 nm(by sonication method to examine its antibacterial effect. NE was able to inactive *Staphylococcus aureus* after 15 min by disruption of its membrane integrity, without any toxic effect on the skin [65]. In a report, antibacterial activity of cinnamon and clove oils on *Staphylococcus aureus* improved 83-166 folds when loaded in a NE with particle size <15 nm. The study revealed that the NE, loaded with essential oil, was beneficial for microorganism resistance compared to conventional formulations of antibiotics [66]. Table 2 expresses NE systems having an antibacterial agent and the main reported findings. From the details, increased delivery of the active ingredient(s) appears to be the most frequent finding. It is already well-known that herbal extracts/ essential oils have the potential to play an important role in fight against antibacterial resistance. However, their efficacy is still an issue [67]. The use of NEs for formulating such products can open new horisons in production of novel antibiotics.

Mycosis is an infection which is caused by different species of fungi. It causes itching, redness, irritation and swelling. Treatment of mycosis commonly requires hydrophobic medications that

Table 1. Infectious bacterial rashes on the skin

Rash type	Source of infection	Main symptoms	Oral/ topical treatment	Ref.
Impetigo	*Staphylococcus aureus, group A Streptococcus.*	Redness of skin, itchy sores	Mupirocin, Minocycline, Dicloxacillin, Cephalexin, Clindamycin, Doxycycline, Trimethoprim, Amoxicillin	[154]
Cellulitis	*Staphylococcus* spp. and *Streptococcus* spp.	Redness and swelling of the skin		[155]
Folliculitis	*Staphylococcus aureus*, viruses, fungus	Swelling/ inflammation of hair follicles		[156]
Erysipelas	*Streptococcus pyogenes*	Redness and swelling of the skin	Penicillin	[157]
Erythema chronicum migrans	*Borrelia burgdorferi*	Growing and red skin patches	Doxycycline, Amoxicillin Cefuroxime	[158]

Table 2. Antibacterial agent delivery using NE system

Antibacterial agent	Ingredients	Preparation methods	Bacterial Sp.	Main finding	Ref.
Mupirocin	Ethyl Oleate, Tween 80, Isopropyl Alcohol and water	High-Speed Homogenizer	*Staphylococcus* spp. *Streptococcus* spp.	Increased delivery (1.54 folds)	[57]
Rifampicin	Oleic acid, Tween 80 and water	Sonication	*S. aureus* and *S. epidermis*	Strong activity on staphylococci	[58]
Penicillin G	Soya phospholipid, soybean oil or miglyol 812, Methanol, phosphate buffer	Spontaneous emulsification	*S. pyrogenesis*	100 % growth inhibition against S.pyrogenesis	[59]
Cefuroxime Axetil	Capmul MCM, Soya lecithin, Deoxycholic acid, Pluronic F127 and distilled water	Spontaneous emulsification	-	Increased delivery	[159]
Linoleic acid	Linoleic acid, water, different surfactant (Tween 80, Lutrol-F68, SLS and BAC)	Sonication	*S. aureus*	Synergic effects between cationic surfactants and Linoleic acid	[63]
Fusidic acid	Phosphatidylcholine, Lauroglycol, Lutrol-F68, TPGS, ethanol, butylated hydroxytoluene and stearyl amine	Homogenization	Methicillin resistance *S. aureus*	improved skin permeability of fusidic acid	[62]
Cleome viscosa essential oil	*C. viscosa* seeds, Tween 80, water	Sonication	*S. aureus, S. pyogenes, E. coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa.*	Considerable bactericidal effect on gram-positive and negative bacteria.	[64]
Eucalyptus oil	Eucalyptus oil, Tween 80, water	Sonication	*S. aureus*	Quick inactivation of *S. aureus*	[65]
Cinnamon and *clove* oils	Cinnamon and clove oils, Brij 35 or Tween 20, water	Spontaneous emulsification	*S. aureus* ATCC 25923 *S. aureus* ATCC 700699	increased antibacterial effects of oils	[66]

suffer from poor water solubility and low skin permeation. NEs/MEs have the potential to raise the efficacy of the active ingredients by overcoming these problems. For example, a NE of sulconazole was developed to improve its skin permeation and antifungal activity. Different variables, including loading capacity, encapsulation efficiency and particle size were investigated to optimize the NE. The results revealed that the optimized NE (particle size: 52 nm, encapsulation efficiency: 87%) managed to improve the drug's penetration rate up to 1.7 folds. Also, the antifungal activity of the drug enhanced against both *Candida albicans* and *Trichophyton rubrum* [68]. As another poorly soluble antifungal medication, Terbinafine HCl was loaded in NE to overcome its limitations in topical uses. The study revealed that the gel form of the NE improved permeation of Terbinafine HCl up to 2.5 folds, compared to the commercial cream. Also, the NE preparation reduced the treatment period from 14 days to 3 days in Wistar rats which were infected with *Trichophyton mentagrophytes* [69]. Likewise, a NE containing naftifine was developed for treatment of tinea. The optimized formulation, having 14 % clove oil and 12.5 mg naftifine, improved its antifungal and antiinflammation activities compared to the commercial medication [70].

Skin infections may also be caused by different types of viruses. NEs have been reported to enhance delivery of the antiviral medication through the cell membrane. For example, a curcumin-loaded NE with particle size of 195 nm was used against variants of HPV-16. While the NE showed acceptable biocompatibility, a considerable cytotoxicity was reported in the group treated with NE containing curcumin which was photoactivated [71].

Pigmentation disorders

Pigmentation disorders include a wide range of heterogeneous diseases that occur due to alteration in density of melanin pigment or number of melanocytes in the skin [72]. These conditions result in abnormal appearance of the skin that are categorized as hyperpigmentation (e.g., melasma, solar lentigines, ephelides), hypopigmentation (e.g., vitiligo, albinism) (Fig. 3). [73, 74]. This section discusses the most common forms of pigmentation disorders and the application of NEs and MEs to treat such diseases.

Hyperpigmentation disorders:

The manifestation of dark lesions on the skin which makes it darker is called hyperpigmentation. The histopathology of hyperpigmentation differs from one disease to another. Regardless of the disease type, visible outcomes from the

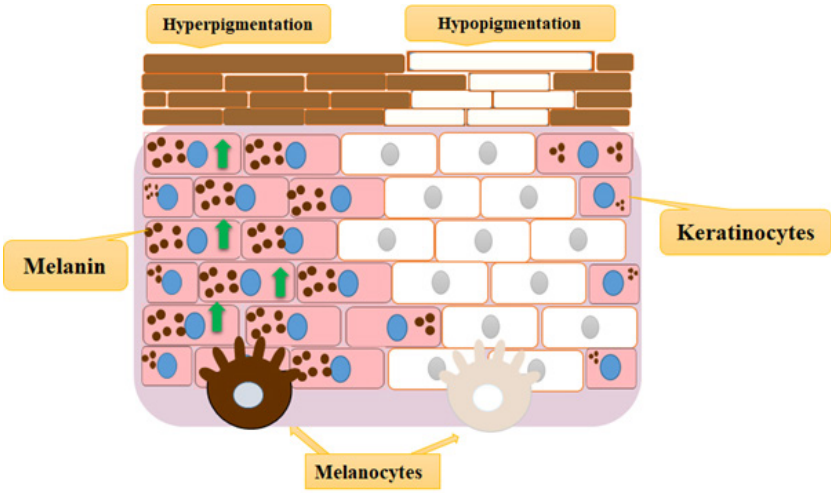

Fig. 3. The schematics of the mechanism

treatment are often time-consuming. The first line in treatment is pharmacotherapy approaches, including topical delivery of hydroquinone, azelaic acid, retinoids and kojic acid along with oral delivery of tranexamic acid and glutathione. The second line includes mechanical methods such as laser therapy and chemical peeling [75, 76].

Melasma (chloasma) is a common hyperpigmentation disorder, which appears with symmetric light to dark-brown lesions on the face. The gold standard local treatment in melasma is hydroquinone. In a study, hydroquinone was loaded into a ME to be compared with the bulk hydroquinone in a topical cream. The release of the hydroquinone from the ME was 87.4% in 24 hr, whilst it was 30% for the cream. Also, the ME (4% W/W hydroquinone) showed less skin irritancy, a common adverse effect which usually happens in long use of hydroquinone [77]. Antityrosinase agents can also be efficient in melasma by preventing conversion of dopamine to melanin. Sompoi (*Acacia concinna Linn*.) extract has shown high antioxidant and anti-tyrosine activity. Nevertheless, these activities deteriorate at ambient conditions. The ME of Sompoi extract successfully preserved the stability and biological functions of the extract after 90 days [78]. Arbutin, a glycosylated hydroquinone, loaded in ME, demonstrated considerable tyrosinase inhibitory effect, proposing a natural-based skin whitening agent [79]. Also, *Punica granatum* extract, as a powerful source of polyphenolic compounds with skin lightening capacity, loaded in a ME, significantly reduced the skin melanin content in healthy volunteers [80]. Likewise, Sripanidkulchai et al. prepared NE of *Phyllanthus emblica* branch extract to improve bioavailability, solubility and stability of the extract. Participants in a clinical trial, who received NE of the extract as a topical gel, showed a significant reduction in melanin indices of their face skin, compared to the placebo group [81]. Azelaic acid is another therapeutic agent in hyperpigmentation disorders. Peira et al. reported that a ME containing azelaic acid could help azelaic acid penetrate the skin and accumulate much better than the solution form of the drug [82]. In addition, azelaic acid-loaded NE containing hyaluronic acid was reported to improve depigmenting effects [83]. Licorice, a natural depigmenting agent, has also been loaded in a targeted NE. The authors claimed that caproyl-hyaluronic acid-decorated NE had a higher whitening effect *in-vitro*, while the ligand itself did not influence the melanogenesis of the tested cell [84].

Hypopigmentation disorders

Vitiligo is a prevalent immune-mediated dermatological condition, distinguished by depigmented macules and patches on the skin, which results from the apoptosis or destruction of melanocytes [73, 74]. The disease is generally recognized as a cosmetic disorder, which negatively affects the psychological status of the patients. Treatment for vitiligo includes taking immunosuppressive agents like topical corticosteroids and phototherapy with ultraviolet (UV) light. Besides, oral antioxidants are recommended to eliminate excess reactive

oxygen species (ROS) and maintain the oxidative-antioxidative balance in the skin [85].

Clobetasol propionate (CP) is a common corticosteroid used in treatment of vitiligo. Due to the lengthy treatment period, dermal side effects such as skin atrophy commonly happen. A ME formulation of CP could overcome the low solubility of CP. Incorporating this emulsion into a carbopol-based gel demonstrated higher retention of CP in the skin and lower irritation compared to the marketed formulation of CP [86]. Besides, repigmentation in patients who received the ME occurred faster than those who received the marketed preparation [87]. Another efficient treatment for vitiligo is psoralens and UV-A phototherapy. A chitosan hydrogel-thickened NE of 8-methoxypsoralen was developed with sweet fennel oil. The NE showed higher retention and penetration into the skin [88]. Also, *Brosimum gaudichaudii* extract, as a rich source of furanocoumarins, was loaded into a physically stable ME. The ME successfully improved the skin permeation of furanocoumarins and reduced their toxicity/ irritation [89]. A combinational approach with NE-gel containing trimethylpsoralen and hesperidin (a flavonoid), followed by UV-A therapy, was conducted on vitiligo model in mice. Findings showed that the NE containing both agents reduced the required UV exposure time. Moreover, it triggered repigmentation in mice faster than the marketed formulation [90]. Furthermore, a ME-based formulation of 8-methoxypsoralen with a suitable chitosan coating improved the retention/permeation ratio. It was found that the ME formulation alone could target the skin better than the chitosan-coated formulation, whilst the latter could enhance skin permeation [91]. Table 5 shows MEs/NEs used for pigmentation disorders, giving details about their active ingredients, excipients, preparation methods, particle size and type of *In vivo* or *ex vivo* investigation.

Wound healing

Wound healing is a complex physiological process that involves homeostasis, inflammation, proliferation and remodeling [92, 93]. The first stage, homeostasis, involves constriction of blood vessels. In this stage, platelets and fibrin scaffolds play an essential role in prevention of bleeding. The second stage is accumulation of white blood cells in the wound through secreting inflammatory factors to prevent infection. The next stage is proliferation that includes re-epithelialization, formation of granulation tissue and neovascularization. The last stage is closing the wound and improving the tensile strength of the tissue. An ideal wound healing system should close the wound quickly, minimize infection and stimulate healing mechanisms [93, 94]. Nanotechnology has opened a new approach to treat/control wounds, provide solutions to accelerate wound healing and offer distinctive properties such as antimicrobial agents [95, 96]. Among different nanoparticles, NEs have been frequently considered for wound healing in the last decades (Table 3).

Table 3. Different NE formulations, used for wound healing

Formulation	Size, Zeta potential	Type of wounds	The most important findings	Ref.
Astaxanthin and alpha-tocopherol with κ-carrageena NE	200 to 250 nm, −28 mV	Diabetic model in rat	Reduction in the wound area as a function of the wound closure rate	[160]
Clove oil NE containing curcumin	93.64 ± 6.48 nm, -1.67 ± 0.11 mV	Excision wound model	Safe and nontoxic/ No signs of inflammatory cells/ Enhanced wound healing effects	[161]
Phenytoin-loaded Alkyd NEs (palm kernel oil)	11- 15 nm, -7.4 mV	HaCaT cell monolayer	Increased proliferation of HaCaT cells	[162]
NE containing *clove* essential oil	29.10 nm, -31.4 mV	Excision wound model in rat	Safe and nontoxic/ No signs of inflammatory cells/ Increased wound healing effects	[163]
Insulin-loaded NE with Aloe vera gel	458 ± 132 nm, -10.2 ± 3.87 mV	Diabetic model in rat	Synergistic effect on wound healing/ Maximum wound closure/ Minimizing wound area	[164]
Achyrocline satureioides (Lam.) DC (Asteraceae) Extract-loaded NE	300 nm, -40 mV	HaCaT cell line	Significant increase of HaCaT viability/ Non-irritative/ Increasing the cell migration at low flavonoid concentrations	[165]
Sea buckthorn seed oil NE-gel	51 and 148 nm, N/A*	Excision and diabetic wound	Improving the retention of the oil on the skin/ Increasing its penetration across the skin/ Improving antibacterial and antifungal effects against *S. aureus*, *P. aeruginosa*, *E. coli* and *C. albicans*/ Enhancing the wound healing activity	[166]
Naringenin- Loaded Chitosan- Coated NE	15.6 nm, -8.3 mV	Abrasion wound model in rat	Low cytotoxicity in fibroblast cells (NIH-3T3), no inhibition in proliferation of the cells, significant improvement in construction of the wound	[99]
NE of flavonoid-enriched oil palm leaf	<100 nm, -24 to -34 mV	Skin biopsy punch (zebrafish)	IC50: 900< mg/l, LC50: 850-1012 mg/l, faster healing rate and higher TGF-β1 expression	[167]

Continued Table 3.

Sesame oil NE containing Levofloxacin	26.3 nm, N/A	Streptozotocin-induced diabetic rats	Reduction in the period of epithelialization, number of inflammatory cells and wound contraction, increases of collagen production and CD31 and TGF-β	[15]
NE Containing Boron and Zinc	<115 nm, −23.9 to − 33.1 mV	Diabetic model in rat	Improvement in wound contraction, stimulation of epithelialization, prevention of epithelial apoptosis.	[168]
NE containing eugenol as oil phase	89.98 nm, −10.05 mV	Irritation study for skin (rat model)	No sign of inflammation, redness of the skin	[169]
Alpha-tocopherol loaded chitosan oleate NEs	220 nm, 56.8 mV	*Ex-vivo* human skin biopsies	Proliferation of keratinocytes and fibroblasts	[170]
Curcumin loaded NE	84 nm, N/A	Incisional wound in rats	No toxicity, complete wound closure after twelve days, increased wound contraction, granulation tissue formation and collagen deposition	[171]
Hydrogels containing soybean isoflavone aglycones-rich fraction-loaded NEs	200 nm, -60 mV	HaCaT cell line (*in-vitro*), Dorsal wounds in rats (*in-vivo*)	Increased viability of HaCaT cells, reduction of the lipid oxidation and level of TNFα (by ~35 %), increasing re-epithelialization (~ 500%) and epithelium thickness	[172]

*: data not available, NE: nanoemulsion

Kazemi et al. investigated the effect of a NE containing lavender essential oil and licorice extract on wound healing. The results of real-time PCR data showed that in comparison with blank and control groups, the NE caused a significant increase in expression of TGF-β1 as well as collagen types I/III genes. Also, increasing activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx) and decreasing lipid peroxidation levels were observed [97]. The effect of propolis and tea tree oil NE loaded with clindamycin hydrochloride on wound healing was investigated in animal model. The size and zeta potential values of NE were 19.42 ± 1.7 nm and -24.5 ± 0.2 mV, respectively. Furthermore, the NE did not show remarkable toxicity against human skin fibroblast cell line. The histopathology results expressed that the NE was effective in wound healing due to antimicrobial activity of tea tree oil as well as re-epithelialization and collagen production properties of propolis [98]. In another study, naringenin-loaded NE, coated with chitosan, had no toxicity *in-vitro* while the animal experiments showed increased wound contraction due to berberine's anti-inflammatory and antioxidant properties [99].

Skin cancers

Skin cancer is a common malignancy that affects about two million people annually worldwide [100, 101]. The most common types of skin cancer include basal cell carcinoma, squamous cell carcinoma and melanoma [102]. Non-melanoma skin cancer, with over 1 million new cases, was the fifth most common cancer in 2018 [103]. Although melanoma is less common than the other two types, it is the leading cause of death in skin cancers, with 57000 death in 2020 [104, 105]. Herein, a summary of some researches on the use of MEs/NEs in treating skin cancers is provided.

The delivery of 3,5,4′-trimethoxy-trans-stilbene, a chemical anticancer to the tumor site, is hindered by skin physiological barriers [106, 107]. This challenge has been resolved by an O/W NE with a particle size of 12 nm. Franz diffusion cell and tumor-bearing mice (C57BL/6 female) were used to investigate skin penetration and anticancer effect [108]. Moreover, the clinical application of camptothecin, a topoisomerase I inhibitor, against cancer is limited due to its insolubility, instability and toxicity [109, 110]. Camptothecin NE was prepared with a particle size of 250 nm using liquid perfluorocarbons and coconut oil. Results showed that the drug release was sustained. Also, a lower dose exhibited more cytotoxicity against B16-F0 melanoma cancer cells [111]. In another study, a castor oil NE containing 5-Fluorouracil, which was gellified by carbopol 934, was reported to have higher efficacy than bulk 5-Fluorouracil on melanoma cancer cells, SK-MEL-5 type [112].

Scaling patches and plaques/papulosquamous disorders

Psoriasis

Psoriasis is a chronic, non-contagious, hereditary skin disease with a global prevalence of 0.51% to 11.43%. The disease can lead to inflamed, thickened, scaly and deformed skin with severe itching [113, 114]. Psoriasis is conventionally managed using systemic or topical therapies. However, the traditional systemic drugs such as methotrexate, cyclosporin A and retinoids may

have important side effects, especially on kidney and liver [115]. Among the topical therapies, emollients and dithranol are associated with fewer side effects but they have low efficiency [116]. Novel drug delivery systems, including NEs, can lead to more efficient therapies for psoriasis by enhancing the delivery of the conventional treatments [117, 118].

Recently, various NE-based antipsoriatics have been formulated on different active ingredients such as betamethasone dipropionate, clobetasol propionate and some natural ones (e.g. turmeric oil and Eucalyptus oil) [119]. A NE formulation for topical co-delivery of clobetasol propionate and calcipotriol was evaluated in an imiquimod-induced psoriatic BALB/c mice model. The authors confirmed significant improvement of antipsoriatic activity of NE, compared to the bulk drug, due to higher uptake of the medicines and higher drug penetration through SC [120]. Topical delivery of two antipsoriatic agents (i.e., Tacrolimus and Kalonji oil) demonstrated an enhanced dermal delivery in NE (4.33 folds) *in-vitro*. Besides, reduction in serum cytokines and improving the psoriatic conditions *in-vivo* confirmed the efficacy of the NE [121]. Another NE was prepared containing chaulmoogra oil and methotrexate. The *ex-vivo* studies, performed by Franz diffusion cell using porcine skin, demonstrated enhanced skin permeation and drug retention in deep skin layers. Moreover, the *in-vivo* studies resulted in high antipsoriatic efficacy, high skin retention, low serum and tissue accumulation compared to oral administration of methotrexate tablets [122].

Also, a NE-loaded polymeric hydrogel showed more than 7-folds increase in penetration of curcumin, compared to the bulk curcumin gel, leading to faster healing in psoriatic mice [123].

An optimized cyclosporine-loaded NE, efficiently carried cyclosporine across rat skin and a synthetic membrane model *in-vitro*. Moreover, *in-vivo* skin analysis revealed a significant improvement in the hydration of the SC [124]. Cyclosporine, loaded in a ME which was gellified using Carbopol 940, showed improved permeation (>24 h) and high drug retention (trapping, 38.92 %) in the skin compared to the cyclosporine suspension [125].

Atopic dermatitis

Atopic dermatitis (AD) is another common skin disorder, characterized by recurrent eczematous lesions and intense itching with substantial socioeconomic effects on the patient's life [126]. MEs/NEs have the potential to provide more efficient treatments [127, 128]. In a study, a stable positively charged NE containing prednicarbate was optimized to treat AD [129]. A ME-based cream of tacrolimus was compared with commercially available ointment for treatment of AD. *In-vivo* studies in hapten-induced murine model of AD showed an enhanced skin penetration. Consequently, dose reduction for the ME-based cream was possible. Histopathological and morphological observations at the site of application also reflected the better efficacy of the ME-based cream [130]. *In-vitro* studies also showed better penetration for NE-based gel containing triptolide (TPL) compared to TPL gel. *In-vivo* microdialysis study showed greater AUC for the concentration-time curve with TLP-NE in comparison with TLP gel. In this study, symptoms of dermatitis and eczema in mice model significantly improved with NE-based gel. The results also confirmed low toxicity and prolonged release of the NE-based gel as a promising transdermal formulation for the clinical treatment of AD and eczema [131].

Acne

ME systems have been developed to treat acne, another common and chronic skin [132]. For treatment of acne, retinoids such as tazarotene [133-135] and adapalene [136, 137], as well as antibiotics such as nadifloxacin [138, 139], have been used in various ME systems.

Physicochemical properties and *in-vitro* release of 8 different MEs containing tretinoin have been compared by Moghimipour *et al.* [140]. A similar study was conducted to evaluate the physicochemical behavior of tretinoin ME. The ME formulation of tretinoin showed an enhanced *in-vitro* release profile compared to the commercial tretinoin gel/ cream [141].

Isotretinoin is another retinoid that has been used in different ME formulations for topical treatment of acne [142-145]. For instance, a ME-based gel formulation incorporating Carbopol 971 was developed for topical delivery of isotretinoin to acne. Spontaneous microemulsification method was used with 8 % isopropyl myristate. The ME-based gel showed improved physicochemical parameters compared to the marketed formulation of isotretinoin [146]. A NE containing tea tree oil as the oil phase and adapalene showed superior anti-acne activity, compared to the conventional

Table 4. Marketed cosmetic products based on NEs

Product name	Marketed by	Uses	Ref.
Red Vine	Korres	Hair sunscreen	[173]
Nanocream	Sinerga	Wet wipes	[173]
NanoVital	Vitacos Cosmetics	Face cleanser	[174]
Vita-herb Whitening	Vitacos Cosmetics	Skin whitening and anti-wrinkle	[175]
Vital NE A-VC	Marie Louise	Anti-wrinkle	[175]
Bepanthol-Protect Facial Cream Ultra	Bayer HealthCare	Anti-pollution, skin hydration and regeneration	[174]
Coco Mademoiselle	Chanel	Prolonged fragrance effect	[173]
Hyaluronic Acid & NE Intensive Hydration Toner	Coni Beauty	Skin hydration	[173]
Phyto-Endorphin	Rhonda Allison	Skin softening and smoothing	[173]
Nano-lipobelle	Mibelle Biochemistry	UVA and UVB filters	[174]

acne preparation, when used clinically [29].

Skincare products

Skin, as the largest organ of the body, has a complex structure consisting of epidermis, dermis and hypodermis. With increasing the skin age, its appearance and functions may change due to various internal and external factors such as ROS generation and UV radiation [147, 148]. The global market of cosmetics is estimated to worth $ 648.3 million by 2026 [149]. Addressing the growing needs for safe, high quality and durable commercial products, many researches in cosmetic products are under way around the world [150].

As skincare or cosmetic products, NEs offer several advantages over traditional preparations: the hydration power of a NE is generally more than the conventional preparations. In a clinical study, most of volunteers who used a NE, appreciated its hydration power as well as texture, freshness and cosmetic results. Eighty percent of the volunteers also stated that they prefer the NE to their usually used products [151]. In a clinical experiment, a lipid-containing, positively-charged NE showed comparable skin hydration and elasticity capabilities with Physiogel® cream, which is a marketed lipid-containing preparation [152]. In addition, improved moisturizing effect of the skin and low irritability have been reported from NE of rice bran oil. The NE also managed to maintain the pH of the skin at normal values [153]. Several companies have developed cosmetic products based on NEs which have been listed in Table 4.

CONCLUSION

Considering the studies mentioned above, it may be concluded that MEs/NEs have the

Table 5. The microemulsion/nanoemulsion systems, reported for pigmentation disorders.

Agent	Ingredients	Preparation methods	Particle size	Excipients	*In vivo* or *ex vivo* investigation	Ref.
Hydroquinone	Isopropyl myristate (IPM) as oil phase, Cremophor EL, Span 20, Span 80 and Tween 20 as surfactant, ethanol as co-surfactant, distilled water as aqueous phase	Spontaneous emulsification	324.9 to 358.0 nm	--	Skin irritations study in healthy BALB-c mice	[75]
Sompoi (Acacia concinna Linn.)pod extract	Tea seed oil, polysorbate 85, ethanol, water	Spontaneous emulsification	239.8 nm	--	--	[78]
Methanolic Extract of the Aerial Part of Arbutus Pavarii Pampan	Oleic acid,water, Tween 80: propylene glycol (PG) as surfactant/cosurfactant mixture or sucrose laurate	Spontaneous emulsification	9.0 to 10.3 nm	--	--	[79]
Pomegranate (Punica granatum) extract	Palm oil, surfactant (Tween 80®) and cosurfactant (propylene glycol), water	Spontaneous emulsification	8.1 ±0.2 µm	--	Evaluation of skin erythema and melanin in 11 male volunteers aged 25–40 years	[80]
Phyllanthus emblica branch ethanolic extract	Isopropyl myristate, Brij®, distilled water	Hot high pressure homogenization	not reported	nanogel:hydroxyethylcellulose base, glycerine, propylene glycol, methylparaben, propyl paraben, and distilled water	Evaluation of melanin index and erythema in 50 healthy Thai volunteers	[81]

Continued Table 5.

Azelaic acid sodium salt	oil phase (decanol:dodecanol), surfactant (lecithin:decyl polyglucoside) and aqueous phase (water:Propylene glycol)	Spontaneous emulsification	30 ± 3 to 35 ± 3 nm	--	Permeation and skin deposition studies in pig ear skin	[82]
Azelaic acid	sorbitan monooleate, poloxamer 407, BHT and rice bran oil, hyaluronic acid and sodium edetate in water	High speed homogenizer	419 nm	phenoxyethanol and caprylyl glycol as preservative	Descriptive clinical sensory evaluation with 16 selected volunteers	[83]
Licorice	wax (semi-synthetic glycerides),oil (soybean oil) and lipophilic surfactant (soybean phospholipids), aqueous phase (phosphate-buffered saline solution) and hydrophilic surfactant (polyethoxylated fatty acid), palmitoyl-glycine-glutamine-proline-arginine (GQPR) from Creative Peptides ,caproyl-hyaluronic acid (HA) from Tenneliderm, polydatin glucoside (PDA) from Induchem and isopilosine	Ultrasonication	46.5 to 84.1 nm	--	--	[84]
Clobetasol propionate	oil phase (Isopropyl myristate), surfactant (Cremophor EL), isopropyl alcohol (co-surfactant)	Spontaneous emulsification	18.3 nm	Carbopol 934P as gelling agent	Draize primary skin irritation test on albino rabbits, *Ex-vivo* permeation studies on healthy male albino Wistar rats skin	[86]
Clobetasol Propionate	oil phase (Isopropyl myristate), surfactant (Cremophor EL), isopropyl alcohol (co-surfactant)	Spontaneous emulsification	18.3 nm	Carbopol 934P as gelling agent	Visualization of penetration in to skin using Confocal Laser Scanning Microscopy and *In vivo* skin hydration study in albino rat skin, dermatopharmokinetic study in albino wistar rats, Pilot clinical study in Six patients with vitiligo	[87]
8-methoxypsoralen	Two foemulation: oil phase (Clove oil), surfactant (Pluronic F68) and oil phase (Sweet Fennel oil), surfactantn (Cremophor RH 40)	High-pressure homogenizer (HPH)	68.1 to 91.3 nm	chitosan with high, medium and low molecular weight as hydrogel- thickened agent	Skin permeation and retention in pig ear skin	[88]
Brosimum gaudichaudii extracts	oil phase (ethyl oleate), surfactants (Labrasol® and Plurol® Oleique), ultrapurified water	Spontaneous emulsification	110.4 to 141.4 nm	--	Skin permeation study with pieces of skin from porcine ears	[89]
Trimethylpsoralen and Hesperidin	Capryol 90, Capmul MCM, Tween 80, Cremophor, Polyethylene glycol 400	Spontaneous emulsification	200-600 nm	Carbopol 934 as gelling agent	*In vivo* studies male C57BL/6 mice to evaluate treatment of the vitiligo-induced subject	[90]
8-methoxypsoralen	oil phase (Ethyl oleate or Oleic acid), Surfactant (EL35 or Solutol or RH40), Cosurfactant (Ethanol or Propylene glycol), water, chitosan derivatives	Spontaneous emulsification	17.30 to 20.04 nm	--	*Ex vivo* skin retention/permeation study in excised porcine skin and Pharmacokinetic study in rat	[91]

potential to increase delivery of the active ingredient(s) to the targeted site, when used topically. The ME/NE is expected to affect the penetration (and bioavailability) of both hydrophilic and hydrophobic drugs, thus, decrease required treatment duration. However, it is worth noticing that various parameters such as the type and concentration of the ingredients, preparation

method, particle size, drug solubility and loading capacity are expected to affect the delivery process and efficiency of the treatment.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

Authors have no conflict of interest.

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