Nanoemulsions: a new trend in transdermal drug delivery

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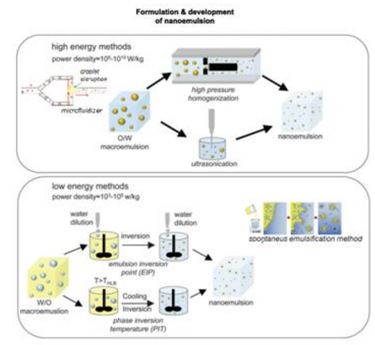
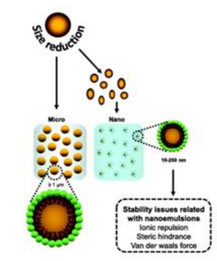
Introduction

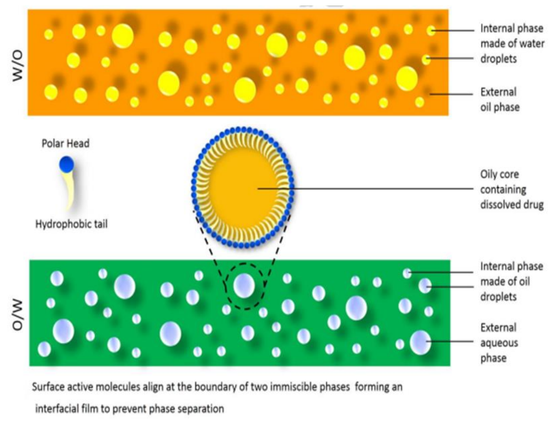
Nanoemulsions (NEs) as transdermal carriers are new delivery systems for relatively large number of active substances. Nanosize of droplets, good kinetic stability, transparency, possibility of applying nanoemulsions on large skin surface and effective permeability of components through skin show great potential of these colloidal systems. To develop these nanocarriers it is important to select the appropriate composition and manufacturing method that ensures complete delivery of the active substance to bloodstream and stability of the system. Surfactants and permeation enhancers, as well as the oil phase, are necessary components of transdermal nanoemulsions because they enable better permeation through skin and delivery of hydrophilic and hydrophobic active substances incorporated in nanoemulsions, in systemic circulation. Transdermal nanoemulsions are still the focus of many studies and scientists are finding new ways to use these innovative, non-invasive, cost-effective nanocarriers in treatment various inflammatory, cardiovascular, infectious diseases, cancer, disorders of central nervous system, etc. (Shaker et al., 2019; Singh et al., 2017). Not all active substances can be delivered by transdermal systems, as they don't have required physical or chemical properties. Characteristics of the active substance suitable for transdermal delivery are: low dose for delivery (below 20 mg per day), molar mass below 500 g/mol, moderate lipophilicity (logP between 1-5), melting point less than 250ºC (Kováčik et al., 2020). The active substances of classes II and IV of biopharmaceutics classification system are ideal for transdermal delivery and many of them are incorporated in transdermal nanoemulsions (Abdelkader and Fathalla, 2018). Many hydrophilic and hydrophobic active substances have been successfully incorporated in w/o or o/w transdermal nanoemulsions (Shaker et al., 2019). Commercialization of transdermal nanoemulsions is not yet well developed but due to the number of clinical trials and patents success is expected in the near future. Transdermal hormone delivery is the future of hormone therapy. Transdermal nanoemulsions with incorporated hormones are in clinical studies (testosterone - Biolipid B2, in clinical trial phase I, estradiol - Nestorone, in clinical trial phase III (Singh et al., 2017; Prasad, 2015). Estrasorb™ and Androsorb™ are products of Novavax Inc. They are transdermal nanoemulsions formulated as micellar nanoparticle emulsion/micellar nanoparticle cream whose active substances are hormones estradiol/testosterone. They are used for treatment of perimenopausal symptoms once daily. In some cases, pharmaceutical technology converts liquid nanoemulsions into semi-solid pharmaceuticals (gels, creams, ointments) and strives to bring these forms to the market (Rai et al. 2018).

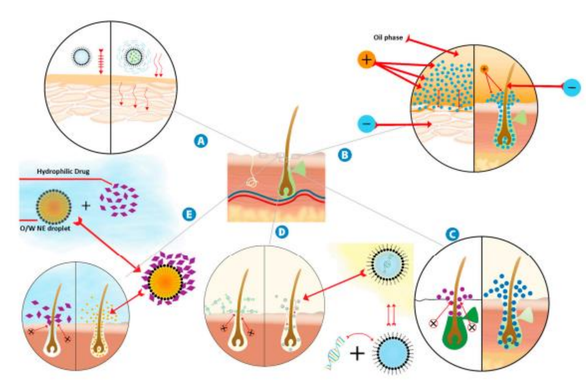




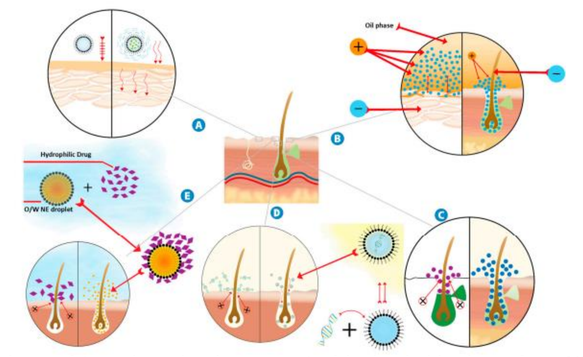
Nanoemulsions as vehicles for transdermal delivery of drugs

Main components of transdermal nanoemulsion are oil and water phase, surfactant, co-surfactant and permeation enhancer. Oil and water phase are very important because they incorporate active substances inside, due to their affinity to lipid or water phase. Role of surfactants, co-surfactants and permeation enhancers are to ensure stability and effectiveness of the formulation (Shaker et al., 2019; Rai et al. 2018). In o/w nanoemulsion, percentage of oil phase is 2-20% (Rai et al., 2018). Surfactants ensure steric, electrostatic and steric-electrostatic stability of nanoemulsion. They can be nonionic, kationic, anionic and "zwitter"-ionic. Nonionic surfactants are very safe in concentrations ranging from 30% to 60%. Surfactants are usually combined with co-surfactants. Role of co-surfactants in nanoemulsion is to help surfactant and increase fluidity and entropy of the system. Surfactants alongside with permeation enhancers disrupt lipid bilayers and form special domains that allow permeation of active substances. Denaturation of keratin filaments can also be a mechanism for enhanced permeation of substances. Surfactants solubilize sebum that clogs pores, which eases active substance transfer through skin into the blood and they can alter pharmacokinetics and pharmacodynamics of active substance (Shaker et al., 2019; Singh et al., 2017). Not all active substances can be delivered by transdermal systems, as they don't have required physical or chemical properties. Characteristics of the active substance suitable for transdermal delivery are: low dose for delivery (below 20 mg per day), molar mass below 500 g/mol, moderate lipophilicity (logP between 1-5), melting point less than 250ºC (Kováčik et al., 2020). The active substances of classes II and IV of biopharmaceutics classification system are ideal for transdermal delivery and many of them are incorporated in transdermal nanoemulsions (Abdelkader and Fathalla, 2018). Many hydrophilic and hydrophobic active substances have been successfully incorporated in w/o or o/w transdermal nanoemulsions (Shaker et al., 2019). Commercialization of transdermal nanoemulsions is not yet well developed but due to the number of clinical trials and patents success is expected in the near future. Transdermal hormone delivery is the future of hormone therapy. Transdermal nanoemulsions with incorporated hormones are in clinical studies (testosterone - Biolipid B2, in clinical trial phase I, estradiol - Nestorone, in clinical trial phase III (Singh et al., 2017; Prasad, 2015). Estrasorb™ and Androsorb™ are products of Novavax Inc. They are transdermal nanoemulsions formulated as micellar nanoparticle emulsion/micellar nanoparticle cream whose active substances are hormones estradiol/testosterone. They are used for treatment of perimenopausal symptoms once daily. In some cases, pharmaceutical technology converts liquid nanoemulsions into semi-solid pharmaceuticals (gels, creams, ointments) and strives to bring these forms to the market (Rai et al. 2018).





Transdermal enhancement of hydrophilic drugs from NE: (A) Increasing drug thermodynamic activity. (B) Modification of surface electrical charge of ionic drugs. (C) Solubilizing of sebum by NE components to facilitate follicular delivery. (D) Pore pathway of large water-soluble molecules loaded in w/o NE. (E) Carrying of small water-soluble molecules into o/w NE for follicular delivery



Mechanisms of transdermal enhancement of hydrophobic drugs from NE: (A) Disruption of lipid bilayer of the *stratum corneum*. (B) Enhancement of transdermal permeation through oil droplet nano-sizing. (C) Binding of positively charged NE to negatively charged skin. (D) Changing drug partition into skin layers. (E) Hydrating skin and the dilation of the *stratum corneum* intercellular channels. (F) Changing the permeation pathway of lipophilic permeants to follicular delivery with an o/w NE

Conclusion

By increasing the concentration of the surfactant and decreasing the concentration of oil phase and using the adequate ratio of surfactant/co-surfactant, stability of nanoemulsion is improved and size of the droplets is reduced. This promotes successful transdermal delivery due to the nanodroplets and low viscosity. Optimal size of droplet of internal phase of transdermal nanoemulsion is below 60 nm. Transdermal nanoemulsions are predominantly formulated in semi-solid dosage forms and this pharmaceutical form provides stability and easier application. Based on many clinical studies and patent research, successful commercialization of nanoemulsions is expected.

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