Macedonian pharmaceutical bulletin, 68 (Suppl 1) 285 - 286 (2022)
Online ISSN 1857 - 8969
DOI:10.33320/maced.pharm.bull.2022.68.03.137
Short communication

Nanoemulsions: a new trend in transdermal drug delivery

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Introduction

Nanoemulsions as transdermal carriers are new delivery systems for relatively large number of active substances. Nanosized droplets, good kinetic stability, transparency, possibility of applying nanoemulsions on large skin surface and effective permeability of components through skin reveal great potential of these colloidal systems. To develop these nanocarriers it is important to select the appropriate composition and manufacturing method to ensure complete delivery of the active substance to bloodstream and system stability. Surfactants and permeation enhancers, as well as the oil phase, are essential components of transdermal nanoemulsions because they improve skin permeation and systemic distribution of hydrophilic and hydrophobic active substances incorporated in nanoemulsions. Many studies continue to focus on transdermal nanoemulsions, and scientists are developing new ways to use these innovative, non-invasive, cost-effective nanocarriers in treatment of various inflammatory, cardiovascular, infectious diseases, cancer, disorders of central nervous system, etc. (Shaker et al., 2019).

Nanoemulsions as vehicles for transdermal drug delivery

Composition of transdermal nanoemulsion vehicle

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. Surfactants, co-surfactants, and permeation enhancers all play a role in ensuring the formulation's stability and effectiveness (Rai et al., 2018; Shaker et al., 2019).

Oil phases used in nanoemulsion are oleic acid, eucalyptol, propylene glycol caprylate, propylene glycol monocaprylate, isopropyl myristate, α-tocopherol, hexyl laurate, caprylic/capric triglyceride and others (Rai et al., 2018; Shaker et al., 2019). The percentage of oil phase in an o/w nanoemulsion 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 (Tween® 20, Tween® 80, Transcutol® HP, Span® 20) are very safe in concentrations ranging from 30% to 60%. Surfactants are usually combined with co-surfactants. Co-surfactants (ethanol, n-butanol, n-hexanol, n-pentanol) assist surfactant and increase the system's fluidity and entropy in nanoemulsion. 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 enhancing substance permeation. Surfactants can alter the pharmacokinetics and pharmacodynamics of active substances by solubilizing sebum that clogs pores, making it easier for active substances to pass through the skin into the bloodstream (Shaker et al., 2019; Singh et al., 2017).

Permeation enhancers promote transdermal delivery through the skin layers (Shaker et al., 2019). Mechanism of action includes influence of these substances on lipids and proteins of *stratum corneum*. They can alter properties of lipids by liquefying them and forming special domains for delivery. Permeation enhancers can also modify protein chains and cause hydration and "swelling" of proteins (Kováčik et al., 2020). Permeation enhancers can be classified in many ways, but the most common classification is by their chemical structure: fatty acids, terpenes, glycols, surfactants, alcohols, amides, phospholipids, sulfoxides and pyrrolidones. Fatty acids, alcohols and sulfoxides are more preferred and are mostly used. Structure of the enhancer plays an important role and can be explained by oleic acid. It is known that *cis* isomer is more active than its *trans* isomer. Therefore, *cis* oleic acid is used as a permeation enhancer that causes swelling of the *stratum corneum* (Kováčik et al., 2020).

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Concentrations of ethanol (which is also co-surfactant) between 50% and 75% lead to formation of new pores, and delivery through them becomes dominant transport route. To demonstrate optimum efficacy, dimethyl sulfoxide concentrations greater than 60% are required (Williams and Barry, 2004). Dermac® SR-38 is oxazolidinone and is designed to mimic ceramides in *stratum corneum*. It is a substance with very low toxicity and is easily removed from circulation. It is non-irritating in concentration range of 1-10%. Ionic liquids (L-proline methyl ester hydrochloride, L-leucine methyl ester hydrochloride) based on amino acids are innovative permeation enhancers that are biodegradable and biocompatible, have minimal toxicity and are important future enhancers for all transdermal systems (Zheng et al., 2020).

Active substances

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 (low solubility, high permeability) and IV (low solubility and permeability) of biopharmaceutics classification system are ideal for transdermal delivery and many of them are incorporated in transdermal nanoemulsions (Abdelkader and Fathalla, 2018). Many hydrophilic (metoprolol, ropinirole hydrochloride, thiocolchicoside, caffeine, inulin, glycyrrhizin, 5-aminolevulinic acid, etc) and hydrophobic (aceclofenac, clozapine, tamoxifen, cumin, imipramine, doxepin, amphotericin B, carvedilol, celecoxib, olmesartan, ketoprofen, glibenclamide, tamoxifen, vitamin E, capsaicin, meloxicam, piroxicam, etc) active substances have been successfully incorporated in o/w or w/o transdermal nanoemulsions (Shaker et al., 2019). Treatment of cardiovascular diseases has been revolutionized by use of transdermal nanoemulsions which have provided great ways to deliver anticoagulants, as well as some antihypertensives and statins (Kováčik et al., 2020; Shaker et al., 2019). Transdermal nanoemulsions have demonstrated outstanding outcomes in cancer treatment, Parkinson's disease treatment, and other clinical research (Shaker et al., 2019). Although commercialization of transdermal nanoemulsions is not yet well developed, success is projected in the near future due to the number of clinical trials and patents. 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 (Prasad, 2015; Singh et al., 2017). Transdermal nanoemulsions, products of Novavax Inc. are 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).

Conclusion

By increasing the concentration of the surfactant and decreasing the concentration of oil phase and using the adequate ratio of surfactant and 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 droplet size for 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 transdermal nanoemulsions is expected.

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