A Microemulsion-Based System for the Dermal Delivery of Therapeutics

By Amnon C. Sintov and Haim V. Levy at NanoDerma Ltd

A new nano-sized dispersion system for topical and transdermal administration of drugs and cosmetic agents has shown promising results for hydrophilic and lipophilic molecules.

There has been a continuously increased interest during recent years in the use of topical vehicle systems that can enhance drug penetration through the skin barrier into the skin or the systemic circulation. In particular, transdermal drug delivery (TDD) is an attractive alternative to conventional oral and injectable dosage forms. Since its introduction about twenty years ago, TDD has generated much hype as a solution for drugs with short biological half-lives, narrow therapeutic windows and poor oral absorption. Transdermal 'patches' are currently available for motion sickness (scopolamine), cardiovascular diseases (clonidine and nitroglycerine), chronic pain (fentanyl, sulfentanil), hormone replacement (for example, estradiol, levonorgestrel), smoking cessation (nicotine), hypogonadism (testosterone) and overactive bladder (oxybutynin). Many more transdermal products for various diseases and disorders are at various stages of research and development.

The quantum and diversity of drugs that can be delivered via transdermal systems are, however, still limited due to the poor loading capability of currently available patches and vehicles, as well as the low diffusivity through the lipophilic layers of the skin, especially of large water-soluble molecules (for example, peptides and proteins). These current drawbacks limit the ability of TDD systems to provide immediate treatment via many drugs that cover a wide spectrum of diseases and disorders. As a consequence, various strategies have emerged to expand the scope of transdermal delivery to hydrophilic molecules and macromolecules (1). These strategies include technologies that are based on electric energy (iontophoresis and electroporation), acoustic energy (sonophoresis) and physical disruption of the skin barrier (microneedles).

Among the various methods, iontophoresis is currently the most advanced technology and is already being used clinically for topical and transdermal delivery of hydrophilic drugs; it may be a promising technique for both small-molecular-weight drugs and high-molecular-weight peptides and proteins. In 1995, Iomed in Utah received approval from the US FDA for iontophoretic delivery of lidocaine hydrochloride 2% and epinephrine 1:100,000 from the US FDA for dermal anesthesia. In 2005, Vyteris (Fair Lawn, NJ) received FDA approval for LidoSite, a pre-filled/pre-programmed iontophoretic delivery system containing lidocaine. Although these commercial lidocaine products are effective, there is still a need to reduce the long delay between drug application and the local aesthetic effect. A combination strategy, such as iontophoresis in conjunction with pre-designed and effective formulation, has already been demonstrated to improve skin penetration of drugs (2-6), and in the near future it may provide a more rapid, more accurate and easier delivery of poorly water-soluble compounds and macromolecules.

MICROEMULSIONS

Hoar and Schulman introduced the term ‘microemulsion’ in Nature in 1943 to define a clear
Microemulsions are, however, complex systems and their integrated microstructures can be influenced by minute modifications and alterations in the type of the components and/or the components’ ratio, as well as by molecular interactions with drugs. Since microemulsions are quaternary systems comprising an oil phase, a water phase, surfactants (usually several) and a co-surfactant with a lot of possible combinations, a huge diversity of microstructures can be constructed.

Microstructures can be conceived to be an ideal vehicle for drug delivery since they provide a long shelf-life due to their thermodynamic nature and infinite physical stability. They have a very low interfacial tension and are formed spontaneously when admixing the appropriate quantities of the components. They also contain very small droplets that can be used as drug carriers and have an enormous surface area that enables a high solubilisation capacity for poorly soluble drugs. This represents a particularly attractive possibility for the use of microemulsions to enhance the efficacy of biologically active compounds by providing a readily-controlled and stable medium for the solubilised components.

Microemulsions are formed (see Figure 1). They have a very low interfacial tension and are formed spontaneously when admixing the appropriate quantities of the components. They also contain very small droplets that can be used as drug carriers and have an enormous surface area that enables a high solubilisation capacity for poorly soluble drugs. This represents a particularly attractive possibility for the use of microemulsions to enhance the efficacy of biologically active compounds by providing a readily-controlled and stable medium for the solubilised components.

Microemulsions are, however, complex systems and their integrated microstructures can be influenced by minute modifications and alterations in the type of the components and/or the components’ ratio, as well as by molecular interactions with drugs. Since microemulsions are quaternary systems comprising an oil phase, a water phase, surfactants (usually several) and a co-surfactant with a lot of possible combinations, a huge diversity of microstructures can be constructed. The characterisation of these microstructures, and their in vitro and in vivo screening (as vehicles for drug administration) are not easy. In addition, many extensive studies during the last decades have been performed on microemulsions using short-chain and medium-chain alcohols as co-surfactants. The inclusion of these alcohols, and the use of high levels of surfactants, have limited their use due to skin irritancy, and have prevented a variety of microemulsion-based products from reaching the market. Thus, to fulfil the great potential of this promising technology, alcohol-free microemulsion formulations with well-selected surfactants and co-surfactants will be sought and applied in medical practice.

THE NANOEMULSION SYSTEM

At NanoDerma, we have developed alcohol-free, non-irritant dermal formulations for the administration of various medications into deep layers of the skin and through the skin into the blood. In our previous publications (7-9), we demonstrated that the new NanoEmulsion system provided improved transdermal and dermal drug delivery properties. Following an intensive research programme, the system was characterised and optimised; the research included tests of the suitability of the system with a drug and its specific application, in vitro skin penetration testing and in vivo drug absorption studies. In all studies, the compositions contained safe and non-irritant inactive ingredients selected from commonly used materials used in cosmetics and pharmaceuticals. The NanoEmulsion system was found to possess a high solubilisation capacity for the tested drugs, due to a very small droplet size and the dynamic and flexible interfacial surfactant film between the phases; this enables migration of the drug in the dispersed system as if it were one continuous phase. This energy-rich system facilitates drug partitioning and diffusion into the skin, and significantly increases its percutaneous penetration. The NanoEmulsion could also be fabricated as transdermal patches by casting in variously shaped moulds; the liquid microemulsion is rapidly cured in the moulds in which ‘easy-to-handle’ patches are formed (see Figure 1).

IMPROVING DRUG PENETRATION: PRE-CLINICAL STUDIES

Lidocaine

The major drawback to local anaesthetic products such as EMLA cream (a commercial product manufactured by Astra, containing 1:1 eutectic mixture of 2.5% lidocaine and 2.55% prilocaine) is the 45 to 60 minutes required after application for the full effect to be noted. To assess the efficacy of the new NanoEmulsion, it was necessary to quantify lidocaine delivery in vivo by short-term monitoring of the disposition of the drug deep in the skin, and the accumulation quantities of the drug in skin layers. It was found that the drug content in rat skin treated with the NanoEmulsion for 30 and 60 minutes was significantly higher than the drug measured after EMLA application (7). This difference was noted in both the epidermis and dermis. When a patch made of the same NanoEmulsion composition was applied for 30 minutes, lidocaine content in the epidermis was comparable with the liquid. Interestingly, however, drug concentrations in the dermis after a 30-minute patch application (at an average value of 4.25g/cm2) were found to be twice those found after application of the liquid NanoEmulsion (average value of 1.92g/cm2).
After demonstrating the potential of the NanoEmulsion system for passive lidocaine delivery, we set out to demonstrate the potential advantages of iontophoretic delivery of lidocaine hydrochloride from the system. Since more rapid onset of local anaesthesia has always been preferable, we made a further attempt to shorten the time of treatment by combining a short-term iontophoresis (5 or 10 minutes) with the topical treatment. In this study (8), the same type of topical NanoEmulsion loaded with lidocaine hydrochloride was further evaluated in vitro and in vivo in combination with short-term (maximum 10 minutes) anodal iontophoresis. The mechanism by which the system contributes to iontophoretic drug delivery is based on its lipophilic nature, which enables increased intercalation of aqueous nano-droplets into the stratum corneum. Charge transport in the microemulsion during iontophoresis is probably facilitated by the flexibility of the surfactant film, allowing the hopping of drug ions within nano-droplet clusters (although this still remains to be fully investigated).

Application of an electric field for 10 minutes appeared to cause significant enhancement of lidocaine permeation through the stratum corneum. We found the combination of the NanoEmulsion formulation with 10 minutes of iontophoresis (electric current density of 1.13mA/cm²) to be the most effective delivery protocol. Both the in vitro and in vivo studies demonstrated that this combination increased the flux, in comparison with that obtained with the aqueous lidocaine solution. The in vivo studies revealed that this combination gave relatively high drug concentrations in both the dermis and epidermis for up to 4 hours. In contrast, application of the aqueous solution/iontophoresis combination resulted in relatively lower drug accumulation with more rapid clearance of the drug from the skin. The advantages of the combined microemulsion/10-minute iontophoresis procedure included significantly increased fluxes, accumulation of a large skin drug depot, short lag times, a possible reduction of irritation (compared with long-term iontophoresis), simplicity and ease of compliance. As mentioned above, the explanation for the phenomenon that the less electrically conducting system (relative to the aqueous solution) – the NanoEmulsion – increased iontophoretic delivery of lidocaine ions may lie in the hopping of ions within nanodroplet clusters, but it still remains to be thoroughly investigated.

Diclofenac Sodium

Diclofenac is a highly effective nonsteroidal anti-inflammatory agent (NSAID) used in the management of acute conditions affecting soft tissue such as tendons, bursa and muscle. Concentrations of the drug in the systemic blood circulation following topical application are considerably lower than following other routes of administration (oral, rectal, parenteral); however, this route is associated with a reduced risk of side effects – in particular, gastrointestinal adverse reactions. A topical formulation – if properly designed to be locally effective (that is, drug is absorbed into the peripheral blood at the site of action) – may be beneficial in minimising the inflammation process with a reduced risk to the patient.

In our laboratory, we challenged this limitation by using the NanoEmulsion vehicle system containing diclofenac, and studied its properties and skin penetration-enhancing ability. It was found (9) that topical delivery from the NanoEmulsion vehicle was highly effective in vivo and in vitro. The transdermal administration of the NanoEmulsion to rats resulted in eight-fold higher drug plasma levels than those obtained after application of the commercial Voltaren® Emulgel cream. Drug plasma levels obtained during 4-8 hours following topical NanoEmulsion application were comparable with the peak plasma level obtained one hour after subcutaneous administration of 3.5mg/kg. The transdermal fluxes of diclofenac were also measured in vitro using skin excised from different animal species. The penetration fluxes obtained following application of the NanoEmulsion to fresh skin excised from different animal species were significantly higher than those obtained by application of the drug in aqueous solution.
Cyclosporine

Cyclosporine A (CysA), a cyclic undecapeptide, is an effective inhibitor of both humoral and cell-mediated immune responses by specifically and reversibly interacting with T lymphocytes. It has been used clinically via oral administration for the prophylaxis and treatment of organ rejection in transplants, as well as in the treatment of immune-related disorders of the skin such as psoriasis; however, its administration is associated with a large number of side-effects. Although the topical administration of CysA for the treatment of skin diseases (without major systemic problems) is an attractive goal, the transdermal delivery of CysA has never been a simple task. This is due to its highly lipophilic nature, its large molecular weight and its cyclic structure.

A NanoEmulsion in the form of a gel containing 1% CysA was fabricated and compared in an in vivo study with a 1% drug solution in polyethyleneglycol (PEG). As seen in Figure 2, while the drug applied with the PEG solution was accumulated only in the epidermis, the new gel delivered the drug quantitatively into the dermis in a controlled and prolonged manner. No measurable CysA levels were detected in the plasma after a 4-hour application, suggesting that the new gel may be a safe and effective vehicle for the therapy of skin diseases with cyclosporine.

Magnesium Ascorbyl Phosphate

In the presence of our oxygen-rich atmosphere, ultraviolet light and other inflammatory insults such as pollution generate reactive oxygen species (ROS) in the skin. ROS, in turn, alter DNA and its repair mechanisms, and trigger cytokine cascades that result in skin aging and carcinogenesis. L-ascorbic acid (or vitamin C) is an essential and most abundant antioxidant in skin, protecting it from oxidation by ROS attack. It is also one of the relatively few topical agents whose effectiveness against wrinkles and fine lines (by boosting skin collagen synthesis) has been proven and supported by many reliable scientific studies. Unlike other animals and plants, in the human (and guinea pig), ascorbic acid is considered as a vital nutrient because the gene necessary for its synthesis in the body has mutated. Despite its importance and effectiveness, the use of L-ascorbic acid in cosmetic and liquid or semi-liquid pharmaceutical products is not practical due to its poor stability; however, to take advantage of its superior skin benefits, several companies have made an effort and synthesized more stable derivatives. Among these, the two most popular in the skin care market are ascorbyl palmitate and magnesium ascorbyl phosphate (MAP). MAP is a water-soluble derivative of ascorbic acid; it is non-irritating and potent after its biotransformation to the vitamin in the skin. However, its hydrophilicity limits its level of skin permeation.

The biotransformation of penetrating MAP in the skin of scorbutic guinea pigs after application of 1% MAP solution...
was found to be negligible at the site of application, probably due to a poor permeation deep into the skin (see Figure 3). When NanoEmulsion containing 1% MAP was applied to the skin of scorbutic guinea pigs, significantly more MAP penetrated into the skin and, more importantly, the biotransformation into active vitamin C was 10-fold higher, with the NanoEmulsion than the aqueous solution.

LOOKING AHEAD: TARGETING UNMET MEDICAL NEEDS

Drug delivery is a dramatically expanding multi-billion-dollar global industry. The number of companies entering the market is rapidly increasing and innovative technologies are emerging at a very fast rate. Non-parenteral drug delivery now seems to be positioned for significant growth. Biopharmaceuticals – in particular peptides and proteins – are susceptible to denaturation and hydrolysis in the gastrointestinal tract, and hence are unsuitable for oral administration. Accordingly, transdermal as well as intranasal delivery of peptide therapeutics is nowadays considered by pharmaceutical companies as an alternative to parenteral administration.

As demonstrated in the pre-clinical studies described above, significant improvements in transdermal and intradermal delivery were achieved with our NanoEmulsion new technology. Hence, this technology platform has the potential for the development of a large number of products for applications in dermatology and phytomedicine, transdermal drug delivery for systemic needs, local anaesthetics, protein and peptide drugs, as well as a DNA protection factor (for example, to prevent melanoma), cosmetic products (cosmeceuticals) for the enrichment of human skin with relatively high levels of antioxidants and other skin-protecting agents.

The authors can be contacted at asintov@bgu.ac.il and hlevydr@netvision.net.il

References