Chapter 2
How to Optimize Drug Delivery in Dermatology?

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Introduction

The skin is the largest organ of the human body in which its main function is to be the protection barrier against the infectious agents, allergens, chemicals, and drugs and against the exit of endogenous substances, such as water. Because of the capacity of the cutaneous absorption, it may be considered a safe and effective way for the injection of several medicines.

The epidermis, the outer layer of the skin, is a divided epithelium into two different areas: a hydrophilic layer containing 70% of water and the stratum corneum which is a hydrophobic layer containing only 13% of water. The stratum corneum is the main barrier for the drug penetration, and it represents the final product of the differentiation of the initiated process on the basal layer of the epidermis with the formation of keratinocytes by mitotic division. It is composed by dead keratinized and flattened cells, which are called corneocyte and are involved by a lipid layer like "bricks and grout." Its main composition is rich in lipids (5–15%) including phospholipids, glycosphingolipids, cholesterol sulfate, neutral lipids, and protein (75–85%), especially keratin [19, 60].

The medicine absorption faces a big challenge which is the skin barrier function that acts by limiting the absorption of many actives. Only few molecules have the capacity to go through this barrier, and the cutaneous bioavailability of most drugs varies from 1% to 5%, therefore being too low. The technique named drug delivery

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consists in finding methods to optimize the cutaneous penetration of the medicine, and this objective can be reached through mechanic, chemical, and physical methods. These techniques provide a raise in the active principles number which can be easily transported through the skin, with a growing importance for dermatology [11, 55, 72].

The drug absorption in the skin can be affected by many factors, such as thickness, temperature, hydration degree, skin cleanliness, blood flux, lipid concentration, hair follicles, sweat glands, race, pH on the surface of the skin, and integrity of the stratum corneum [18, 79].

The drug administration through the skin can be achieved via topical in which the main objective is a local therapeutic action and the transdermal via that has a systemic therapeutic action. One of the biggest advantages of the topical drug administration is to have a direct action in the target or very close to it, this way needing least amount of active substance and with fewer side effects.

A substance topically applied has basically three possibilities of penetrating in the intact stratum corneum of the epidermis through the transcellular or intracellular vias (directly through the cells), the intercellular (around the cells), and the cutaneous attachments (sweat glands, sebaceous glands, or hair follicles). There might be drug permeation through a combination of these vias, the highest flux being established by the physicochemical properties of the molecule.

Once it has passed the stratum corneum, the active substance may have a target in some of the layers of the epidermis and the dermis, or it may be absorbed and have a systemic action. In the transepidermal penetration, the molecule passage happens through the epidermis layers. More externally there is the stratum corneum, made of rows of corneocytes soaked in lipid intercellular layer, representing the main cutaneous barrier to the substance penetration. The intracellular passage of the substances happens through the keratinocytes that allow the hydrophilic or polar solute transportation. However the transportation through the intercellular spaces allows diffusion of lipophilic or non-polar solutes by the lipid layer [55, 58, 68].

As a result of the stratum corneum dead nature, the solute transportation through this layer happens mainly by passive diffusion accordingly with Fick's law.

By the transcellular via, the drugs go through the phospholipid membranes and the cytoplasm of the stratum corneum keratinocytes; however they face a significant resistance to the penetration, once they need to go through the phospholipid membrane of each cell, the hydrophilic components of the keratinocytes, and again the phospholipid membrane. Though this via is the most direct one, the most used via is the intercellular, where the drugs go through the existent spaces between the different cells of the skin. The existence of hair follicles in the skin makes them also a via for the drug penetration. But, since the area occupied by the hair follicles and the sebaceous glands is small (approximately 0.1% of the area of the skin surface), this is a factor that limits the available area for the medicine transportation [9, 12, 17, 40].

The intercellular via involves the drug diffusion through the extracellular lipid layer. But this route has an obstacle because of the stratum corneum barrier which is highly waterproof ("bricks and grout") for most of the molecules, being that just lipophilic drugs of low molecular weight penetrate in this via.

Since the skin represents an efficient barrier to the penetration of molecules, many chemical (passive) and physical (active) methods are being developed to change the stratum corneum barrier properties and raise the permeability.

The strategies to develop the drug penetration vary since a simple occlusion to the use of chemical or physical methods and technologies, or the combination of them. These methods may include the application of many energy forms (e.g., heat, sound, light, electric, magnetic, etc.) or break, reduce, or weaken the stratum corneum barrier by mechanic means [64].

The chemical methods are represented by substances that raise the drug diffusion through the stratum corneum and are known as chemical promoters of permeation. The most common chemical substance is water, due to the stratum corneum hydration, usually when it accumulates during the occlusion process of the skin. After 24–48 hours of occlusion, the corneocytes swell, the intercellular spaces distend, and the lacunar network becomes dilated. This gap distention creates "pores" in the interstices of the stratum corneum through which the substances can penetrate more easily. As examples of the chemical promoters of permeation, the solvents (ethanol, methanol, chloroform, acetone, and detergents) can extract the lipids from the stratum corneum, maximizing the drug penetration in the skin [44, 64].

The physical methods include the ones that destroy the stratum corneum barrier and the ones that act through an external force impacting the active ingredients in the skin. These techniques provide an increase in the number of the active ingredients which may be efficiently transported through the skin, with a growing importance for dermatology. As an objective to improve the cutaneous permeability and the substance penetration through the stratum corneum, many techniques have been associated with the transdermal via of drug absorption, such as ultrasound (cavitational and non-cavitational), iontophoresis, electroporation, microdermabrasion, thermal ablation (laser, microneedled, radio frequency), and medicine microinfusion in the skin using the tattoo machine and microneedling [1, 5, 70].

Factors That Influence the Transdermal Drug Delivery

Physicochemical Properties of Permeation [23, 38, 74]

- Permeation coefficient: The transcellular route predominates for the most hydrophilic molecules.
- Molecular size: There is an inverse relation between the transdermal flux and the molecular weight of the molecule. The molecule that goes through the skin barrier tends to have a molecular weight between 100 and 500 dalton.
- Solubility/fusion point: The lipophilic molecules tend to permeate the skin faster than the hydrophilic molecules.
- Ionization: Only the ionized form of the drug can permeate significantly by the lipid barrier.

Physiological and Pathological Conditions of the Skin [23, 38, 74]

- Lipid film: The lipid film on the skin surface acts as a protective layer to avoid the skin humidity loss and to help maintain the function of the stratum corneum barrier.
- Skin hydration: The hydration may be reached simply by occluding the skin with plastic film, leading to a sweat accumulation and improving the active penetration.
- Skin temperature: The increase in temperature increases the permeation rate of the skin, due to the energy availability needed for the diffusibility.
- Regional variation: The difference between the nature and thickness of the skin barrier can cause a permeability variation.
- Individual skin metabolism: The catabolic enzymes present in the epidermis may turn the drug inactive by the metabolism and slow down the drug topical bioavailability.
- Skin barrier properties: The physiological pH of the skin is acid and is between 4.2 and 5.6. It varies with age, being higher in the newborns when compared to adult skin. Substances as acid as the skin acidity are more absorbed, for they are less ionized.
- Body skin: The skin of the genital region usually provides the most permeable spot for the transdermal drug delivery. The skin of the head and neck is also relatively permeable if compared with other spots of the body like arms and legs. Intermediate permeability for most drugs is found in the upper body.
- Pathological injuries of the body: Injuries that change the stratum corneum continuity, removing part of the protection barrier, increase the permeability due to the vasodilation increase.

Methods That Optimize the Drug Delivery in the Skin

Mechanical Methods

Adhesive Tape

One of the easiest mechanical methods to improve the drug penetration in the skin is using the adhesive tape, inserted in transdermal studies in early 1970s. In this method, the outer layer of the skin, the stratum corneum, is progressively reduced in thickness by a series of tape application and removal. The theoretical considerations based on the first diffusion law of Fick show that the flux through a membrane is inversely proportional to the membrane length or thickness. If the stratum corneum thickness is reduced by the tape application, there will be an increase of the drug diffusion.

Massage

Studies suggest that massage can be a useful tool in the increase of the transdermal drug delivery. The skin heating may increase the stratum corneum permeability due to structural changes in the lipids by the temperature increase (20–40 °C) [69].

Lademann et al. investigated the nanoparticle transportation in hair follicles on pigskin in vitro and suggested an ideal size (300–600 mm) for the particles to penetrate in the follicles, based on the hair cuticle thickness. When the massage was applied, the particles penetrated more deeply in the follicles and remained there for 10 days. The hair follicles act as an efficient vessel for the long-term drug storage if compared to the stratum corneum, creating a possibility of a sustained drug delivery [43].

Skin Abrasion

The skin abrasion refers to the skin surface layer removal by abrasive methods. These methods may include rubbing the skin with electrical sand paper or devices that use abrasive spheres, like a process of "sandblasting" using a flux of crystalline particles such as aluminum oxide. The process was used for the skin rejuvenation but also to increase the penetration of the topically applied substances. The skin abrasion has demonstrated to increase the delivery of a variety of hydrophilic molecules in the skin (caffeine, acyclovir, 5-fluorouracil, vitamin C, aminolevulinic acid, small peptides, and vaccines) [21, 24, 26, 48].

Chemical Methods

The chemical methods act by maximizing the drug penetration in the skin, through mechanisms that change the lipid structure of the stratum corneum, including solvents (propylene glycol, DMSO – dimethyl sulfoxide), esters of fatty acids (oleic acid), and surfactants. These compounds interact with the stratum corneum lipid layer to change its nanostructure and, this way, to increase the skin permeability by many mechanisms: (1) interruption of the stratum corneum lipid organization, turning it permeable (such as the example of the fatty acids, DMSO, and alcohol); (2) extracting the lipids, turning the layer more permeable through the formation of water channels (DMSO and ethanol); and (3) interacting with the corneocyte keratin and opening the protein structure, turning it more permeable (e.g., DMSO, ionic surfactants) [45, 56, 60].

Though there are no ideal permeation chemical promoters yet, these must present the following properties: be pharmacologically inert, nontoxic, non-allergic, non-irritating; have immediate and reversible action; and must allow the drugs to

penetrate the skin but, at the same time, need to avoid the loss of body fluids, electrolytes, and other endogenous substances [17].

However, only a small number of chemical potentializers have demonstrated to induce a significantly therapeutic improvement in the drug transportation. These are often associated with skin irritation or toxicity when present in high concentration and with a longer time of skin exposure.

Physical Methods

The physical methods to increase the cutaneous permeability include the ones which destroy the stratum corneum barrier and the ones that act through an external force impacting the active ingredients in the skin. These techniques provide an increase in the number of the active ingredients which can be efficiently transported through the skin, with growing importance for dermatology.

Electroporation

In electroporation the cells are temporarily exposed to high intensity of electrical pulses that lead to the formation of watery pores in the stratum corneum lipid bilayers, allowing the drug diffusion in the skin. The treatment uses high voltage electrical pulses (50–500 V) for a short period of time (milliseconds) with the objective to increase the drug transportation of high molecular weight (until 40 kDa) [69]. The best fluxes have been observed with synthetic molecules and small macromolecules (<10 kDa), for example, the lidocaine. It has also been used successfully to improve the molecule permeability with different lipophilicities and sizes, including the ones with high molecular weight (proteins, peptides, and oligonucleotides) [37].

The electroporation in the skin has the benefit of being minimally invasive and usually well tolerated. The gene transference by electroporation has been used successfully to deliver genetic material in the in vitro cells as well as the in vivo cells [20, 37].

Iontophoresis

The iontophoresis is a noninvasive technique based on the application of a low intensity electrical current (until 10 V) to facilitate the drug permeation with the help of two electrodes put on the skin surface, through an electrolyte solution which contains the drug. The main changes in the skin after the iontophoresis are the increase of stratum corneum hydration and a decrease of the skin electrical resistance. The iontophoresis applications can be therapeutic and also a diagnostic method to control the levels of blood glucose [1, 69]. The iontophoresis is used with ionizable drugs, and it is more effective to molecules with a low molecular weight.

The iontophoresis disadvantages are the difficulty of the drug stabilization in the means of application, the complexity of the drug release system, and the prolonged cutaneous exposure of an electrical current. Clinically the iontophoresis has been used to treat hyperhidrosis and deliver the lidocaine to relieve the pain and pilocarpine to induce sweat (as a diagnostic test) [64].

The iontophoresis used to be applied in dermatology to treat patients with hyperhidrosis has been practically abandoned [16, 69].

Ultrasound

The ultrasound technique (sonophoresis, phonophoresis, or ultraphonophoresis) increases the drug permeation in the skin due to an increase of the drug therapeutic concentrations on the selected spot. The use of low-frequency ultrasound, between 20 and 100 kHz, has proven to be a promising technique in increasing skin permeability, facilitating the macromolecules and hydrophilic drug permeation through the epidermis, dermis, and cutaneous attachments. The mechanism involves a lipid rupture of the stratum corneum allowing the drug to go through the skin [49].

In this technique, the drug is associated with a coupling agent (gel, lotion, oil) which helps to transfer the ultrasound energy to the skin, leading to the stratum corneum rupture and supporting the transdermal absorption of the drugs [47, 49].

Traditionally, the ultrasound used in high frequencies ($f > 1$ MHz, therapeutic echography) was a popular choice for the sonophoresis in the physiotherapy treatment. The sonophoresis was used to facilitate the topical delivery of medicine in polyarthritis treatment [1].

With the use of low frequencies (<1 MHz), the ultrasound can be used to make bubbles, known as "cavitation." The cavitation bubbles oscillate creating shock waves on the skin and then creating submicroscopic defects in the stratum corneum. These defects increase the skin permeability for water-soluble molecules and some macromolecules. Recent studies show that cavitation is a mechanism which maximizes the transdermal drug delivery result in the ultrasound treatment [47, 49, 59].

Microneedles

The needles create a duct in the skin that allows substances (from small hydrophilic molecules to macromolecules) to penetrate. Used in isolation or with other methods, the microneedles have shown to be a promising method in many clinic applications, such as insulin administration, peptides, genetic material, and also transcutaneous immunization [73].

The microneedling is a fundamental tool so that the product used as drug delivery can act on the dermis in enough quantity to reach the results quickly and effectively. The technique provide a stratum corneum rupture, and that is microscopically proven by the channel visualization and increase in the transepidermal water loss (TEWL) (Fig. 2.1). Consequently, there is a hydrophilic molecule, and

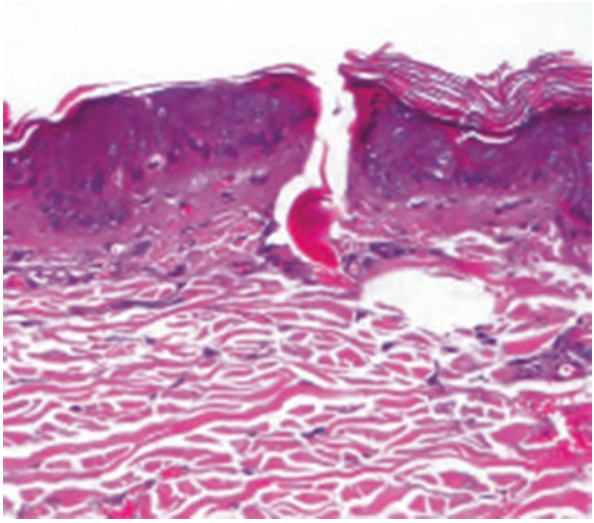

Fig. 2.1 Micro-channel created after the stratum corneum disruption, reaching the papillary dermis, with 1.5 mm microneedles. Histological section of swine skin stained by hematoxylin and eosin with a total increase of 40×. (Figure: Personal file Dr. Luiza Pitassi)

macromolecule increased permeation in the applied formulations after the perforations by the microneedling. The duration of the drug delivery is limited by the lifetime of these pores, and it depends on the area of skin treated, on the drug solubility in the delivery vehicle, on the drug diffusion capacity in the pores, and other factors [25, 29, 61].

The micro-channels facilitate the drug delivery in a very efficient way and can increase in until 80% the absorption of bigger molecules.

The microneedling technique makes thousands of controlled microscopic microperforations in the papillary and reticular dermis. The objective is to perform a mechanical stimulation of the dermis, leaving the epidermis intact, promoting the collagen formation, and increasing the angiogenesis. A dermal vasodilation happens, and immediately there is a keratinocytes migration to restore the epidermal damage, resulting in a cytokine liberation such as interleukin-1, interleukin-8, interleukin-6, TNF-α, and GM-CSF [6, 50, 65].

The microneedling can also be useful to improve the ALA (aminolevulinic acid) or MAL (methylaminolevulinate acid) penetration in the photodynamic therapy (PDT), being a safe and effective method. This association produces superior results when compared to the conventional photodynamic therapy with the use of the MAL photosensitizer agent to improve the skin damaged by light and the results of the actinic keratosis treatment [71, 80].

The microneedling combined with the drug delivery in embryonic stem cells (hESC-EPC CM) showed to be effective in reversing aging signs and can also be a great option for skin rejuvenation. An accomplished study with human embryonic stem cells in vitro showed a significant increase in the proliferation and migration of dermal fibroblasts, besides the epidermal keratinocytes, supporting collagen synthesis by fibroblasts [46].

The microneedling technique can be associated with the drug transdermal administration for chest rejuvenation providing an improvement on global appearance of the skin on the anterior chest region, with high tolerability and satisfaction [39].

Clinical studies performed in diabetes patients showed an increased insulin pharmacokinetics after the injections with microneedles in the skin when compared to the conventional subcutaneous infusions [62].

In vitro experiments showed that the use of microneedles could increase the permeability in the skin, enhancing transdermal delivery of a variety of substances, including oligonucleotides, insulin, vaccines, proteins, DNA, and human growth hormone [14, 42].

Fractional Ablative Lasers

Recently, the use of lasers as drug delivery promoters has shown excellent results for a homogeneous and controlled skin medicine delivery. Since the beginning of its therapeutic use in the last decade, the ablative Erbium 2940 nm and CO2 10.600 nm lasers have been useful in the skin photoaging and scar treatments. As both have great affinity with water, they are ablative lasers, removing the epidermis and promoting residual sharp heat, which makes the water contained in the dermis heated until approximately 100 °C [13, 41, 51].

The fractional ablative lasers are used mainly to soften wrinkles, photoaging, cutaneous laxity, and scars, without the disadvantages and risk related to the long exposure of the traditional ablative laser epithelialization. With the fractional laser, a big part of the skin remains intact and surrounded by microablation columns. With this, the postoperative has gotten less intense and shorter, besides the fact that there is lower risk of adverse effects [3].

The ablative lasers remove the stratum corneum without damaging the deeper tissues, forming micro-channels called microthermal zones (MTZ) that increase the hydrophilic and lipophilic substance permeability (Fig. 2.2). Both lasers facilitate the drug delivery through the MTZ and also through thermal effect of the laser in the tissue. The Er:YAG 2940 nm laser has bigger affinity with water, allowing a more superficial penetration and minimum heat production. The CO2 10600 nm laser penetrates more deeply and produces higher heat quantity. The characteristic of the fractional ablative laser is to act through tissue ablation columns surrounded by coagulation tissue [22, 31].

These channels penetrate the stratum corneum facilitating the drug delivery of substances applied on the skin. In vitro studies evaluated the CO2 10600 nm laser as well as the Er:YAG 2940 nm with different formulations containing vitamin C showing the increase of over 200 times in the active penetration when compared to intact skin [33]. A study conducted by Huang et al., in 2013, with three different forms of stabilized vitamin C evaluated the ascorbic acid permeation after the CO2 ablative laser application, demonstrating that this laser is effective in delivering vitamin C to the skin [34].

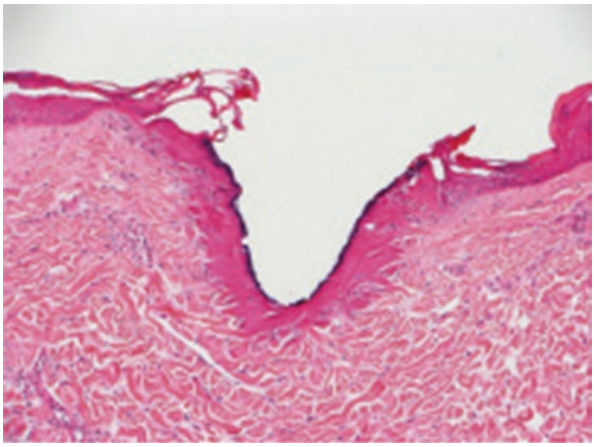

Fig. 2.2 Demonstration of the fractional ablative laser irradiated on the skin, forming micro-channels called microthermal zones (MTZ) that increase the hydrophilic and lipophilic substances permeability. (Figure: Personal file Dr. Luiza Pitassi)

In 2016, Waibel et al. evaluated the use of CO2 laser for the drug delivery of a non-sterile formulation containing 15% of vitamin C, 1% of vitamin E, and 0,5% of ferulic acid in serum vehicle and demonstrated that the hemiface in which the formula was applied showed faster healing. There were no adverse effects reported resulting from the applied formulation [77]. Recently, reports about the functional and quality improvement of traumatic scars, including keloids, have emerged in the literature with the use of fractional laser. In atrophic scars, a depth decrease was observed, that is, volume or surface irregularity improvement. In two cases of burn sequels, the use of the CO2 fractional laser provided the contracture relaxation and surface irregularities and color and texture improvement. In post-traumatic or pathological scars, there are reports about texture, tone, and skin appearance improvement, with low incidence of dyschromia, leading the authors to conclude that it is a safe and effective technology for the scar treatment in general [4, 32].

Recent studies demonstrate the topical application of poly-l-lactic acid after the CO2 fractional laser for the atrophic scar treatment [67].

Another article showed the use of ablative CO2 fractional laser for the hypertrophic scar treatment with application of drug delivery containing triamcinolone 10–20 mg/ml immediately after. There was a considerable scar improvement after 6 months evaluating the following parameters: global improvement, atrophy, and dyschromia [76].

Mahmoud et al. described the use of CO2 fractional laser followed by botulinum toxin application in a topical way as drug delivery in the periorbital area in split-face study. The evaluation, 30 days later, showed a significant improvement on the side that was associated with the botulinum toxin application [54]. Similar results were described by Zhu et al. in 2016; the topical application of the botulinum toxin as drug delivery after CO2 fractional laser in the facial areas chosen by randomization was compared to the saline solution application after the laser [82].

The drug delivery technique assisted by laser has been used a lot in photodynamic therapy (PDT). The PDT is an effective treatment for superficial skin cancers

non-melanoma, actinic keratosis, and acne. The thicker lesions have shown to be more resistant to the TFD due to low depth penetration of the topical photosensitizing agents. An in vivo study using human skin revealed that the ALA and MAL often do not penetrate the depth of the tissue above 1 mm. The pretreatment with the laser in the skin can increase the penetration of these photosensitizing agents in the case of Bowen disease, reducing the incubation time without compromising the treatment efficiency [30].

The most used and studied substances for the drug delivery with laser are vitamins C and E, ferulic acid, hyaluronic acid, polylactic acid, botulinum toxin, methotrexate, 5-fluorouracil (5-FU), imiquimod, ingenol mebutate, minoxidil, growth factors, MAL, and ALA [10, 27, 30, 33, 54, 67, 77].

Besides that, the technique is an excellent association with the laser effects for rejuvenation and dermatological disease treatments.

Fractional Microneedled Radio Frequency

Another ablation method of the tissue associated with the drug delivery technique is accomplished by radio frequency with needles. In this procedure the energy application under the high-frequency alternating current form (~100 kHz) is performed by thin needles in the skin, with the formation of micropores (Fig. 2.3) that allow the hydrophilic drug and macromolecule transport, being used with the drug delivery technique for the same indications as the ablative laser [63].

Issa et al. (2013) evaluated the efficiency, safety, and satisfaction of the patients treated with fractional microneedled radio frequency associated with 0.05% retinoic acid on stretch marks on the breasts. The retinoic acid drug delivery was performed through an ultrasound device with acoustic pressure waves. There was significant

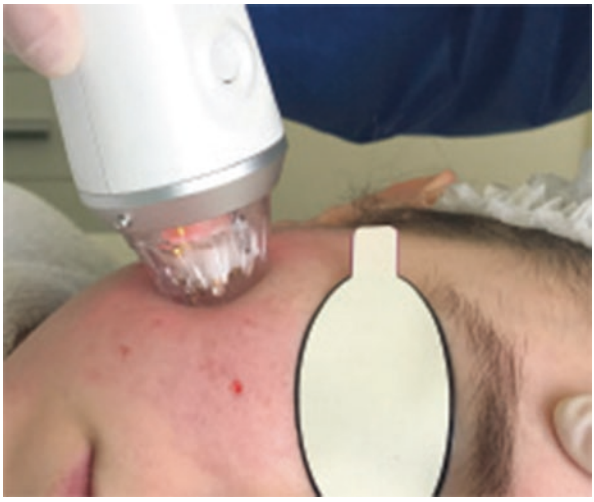

Fig. 2.3 Demonstration of the fractional microneedled radiofrequency application in the facial skin. (Figure: personal file Dr. Luiza Pitassi)

improvement in the treated stretch marks' appearance in all the patients, with low incidence of collateral damage and a high level of patient satisfaction [35].

In another study conducted by the same author, the fractional ablative radio frequency was used in the hypertrophic scar treatment associated with the ultrasound with acoustic waves. The objective of ultrasound use was to increase the active permeation, and in this case, the drug delivery was performed with triamcinolone acetonide. The result of this study was a complete resolution of the scars with only one treatment session [36].

Transdermal Adhesive Systems

Transdermal Patches

The transdermal patches act in the skin by promoting a long release of the drug with the objective to keep the plasma concentrations constant throughout time. The development of these systems is considered a multidisciplinary activity that involves a drug selection, the development of the most suitable therapeutic system taking into account the physicochemical properties of this drug, and in vivo and in vitro permeation studies, besides the patches' stability [66].

The main advantage of the transdermal patches is to provide an ongoing release of the drug, without the occurrence of plasma peaks, this way decreasing the drug adverse effects. For a better absorption, the molecular weight of the drug should not exceed 400 Da. The molecular size is inversely proportional to its cutaneous diffusion; in other words, smaller molecules diffuse better in the skin. The proteins and other macromolecules as the peptides are not indicated for the administration in transdermal adhesive systems because they present a high molecular weight [8].

Though they have a great potential to allow the drug permeation, the transdermal adhesives present a big limitation, once they only allow administrating lipophilic drugs of low molecular weight. The use of chemical permeation promoters and nanotech systems has been studied as a way to increase the spectrum of the transdermal route [17].

Nanotechnology

Currently, new technologies for dermal and transdermal nanoparticles applications are being used in dermatology, such as liposomes and other vesicular systems. These new drug transporter systems optimize the formulation, maintaining the drug molecular structure. They present, among many other advantages, the increase of the substances' bioavailability facilitating the cutaneous permeability and directing them to the tissue or target organ [28].

The nanomedicine has a main objective to create a drug delivery system with great efficiency, in specific targets, minimizing possible secondary effects. This science dedicates itself to research, developing and manipulating material, systems, and nanometric dimension devices, comprised between 1 and 1000 nm [15, 53].

The nanotech is the material engineering that uses the nanoscale for technological or scientific applications. The nanoparticles have many forms (spheres, rods, dendritic) and can be soft or hard, soluble or insoluble [15]. For being useful in therapeutic applications, the nanoparticles must penetrate the cutaneous barrier, deliver the material, and be eliminated from the body without damages. The researchers study the conditions in which the nanoparticles can penetrate the stratum corneum barrier and how the physicochemical properties of the nanoparticles can influence the penetration, the systemic translocation, and toxicity [7, 75].

The liposomes, for example, are nanometric vesicles containing lipid bilayers made by phospholipids, with similar structure of the cellular membrane, designed for the transcutaneous hydrophilic and lipophilic drug administration. The liposomes were the pioneers in nanotech applicability in cosmetic area. The well-succeeded nanomedicine application was already shown in many neuroinflammatory disease, cancer, and rheumatoid arthritis studies, besides many other disorders [52, 53, 78].

The advantages related to the substance placement through the nanotech are countless, for they not only allow the substance transport but also can protect these substances from oxidation reaction, hydrolysis, and photolysis. This way, the nanotech provides tools that allow more stable formulation production during its use and storage. For the effective therapeutic use, the nanotech must be capable of breaking the stratum corneum, and many techniques have been used to facilitate this penetration, such as ultrasound, electroporation, ablative laser, and microneedles. The nanotech and its therapeutic applications in dermatology are growing research areas [15, 57, 81].

Conclusion

Many methodologies have been researched as an objective to improve the drug permeation in the skin. The advances in biotechnology established bases for promising molecular targets, potent and highly specific therapies. The use of nanotechnology in the development and production of drug delivery systems in dermatology has been highlighted lately. Recent studies show that hair follicles can be a great medium to increase the drug permeation efficiency. The genetic therapy has been considered one of the most promising therapeutic ways of drug delivery [2, 44].

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