Drug Delivery in Dermatology

Fundamental and Practical Applications

Célia Luiza Petersen Vitello Kalil
Valéria Campos
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I dedicate this book to my family, Roberto, Pedro, and Carolina, who are essential in my life, for their constant understanding and for being the pillars to my personal, intellectual, and professional growth.

To my parents, my eternal love.

To my fraternal friend Dr. Valéria Campos, who constantly encourages my research and "pioneering" studies with her tireless personality in search of new discoveries, discoveries that, once again, led us to accomplish another book. All my gratitude and affection to this precious friend.

– Célia Luiza Petersen Vitello Kalil

I dedicate this book to Paulo, the love of my life, who is my safe haven at all times, especially for unrestrictedly understanding the countless hours I have been absent; to my parents, Miltes and Adhemar (in memoriam), with all my love and gratitude; to my sisters, who always help me to be a better person; to my beloved nieces and nephew, who always recharge my happiness; to my friends and colleagues, who have

encouraged me every day and offered me support at critical moments.

I also dedicate this work to my sister and friend Célia Kalil, who is a great force and inspiration in my life and the one I hold mainly responsible for making my dream come true.

– Valeria Campos

Introduction

Dermatology, the specialty that I have chosen to practice as a doctor, has shown itself to be increasingly innovative, with continuously growing therapeutic possibilities in the search for treatment of our patients.

Accompanying this constant evolution allows us dermatologists to act more and more as scholars and researchers of the innovations to our approaches. Studies and research are basic, essential, and extremely important elements for us to learn the adequate practice of our therapeutic resources and to carry them out with medical ethics principles.

Thus, we become not only prescribers, but demanding experts, and we seek to practice dermatology based on scientific evidence, deepening our knowledge for this purpose.

Drug delivery, or transepidermal/dermal delivery of drugs in therapies through the skin, has become a choice of therapeutic complement with several opportunities of use within dermatology, providing deepening of our knowledge so that its application and use are carried out on scientific basis.

With this purpose and counting on the instructive, professional, and personal partnership I share with Dr. Valéria Campos, co-author of this book, we approach this dermatological therapeutic modality that encompasses the combination of methods used within the variation found in dermatology.

Therefore, with the contribution of colleagues with technical-scientific dermatological experience, we seek to clarify and elucidate knowledge in an objective way so that the drug delivery technique can be applied with full knowledge and ethics.

We hope that this book will be useful and enlightening to read, because we have written it with great care for this purpose.

Célia Luiza Petersen Vitello Kalil

To our employees Simone Guarnieri, Lidiane Terron, and Aldina Cristina Sousa Castros, thank you for your dedication.

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Chapter 1
Understanding Skin and Drug Delivery

Clarissa Prieto Herman Reinehr, Laura de Mattos Milman, and Valéria Campos

Introduction

The skin accounts for approximately 15% of an adult's total body weight. With a surface area of approximately 2 m^2, it provides a barrier to the entry and exit of numerous substances in the body; acts as an effective protection against harmful substances, microorganisms, and ultraviolet radiation; and is also fundamental in body immunology and homeostasis, preventing dehydration and loss of essential minerals [1].

The epidermis, more specifically the stratum corneum, is the main limiting factor for topical drug delivery [2]. The current tendency is to consider it as an interface that can be manipulated, so as to allow the delivery of the drugs applied to it as desired [2].

The topical route of administration presents some advantages in comparison to the oral or parenteral routes: there is no first pass metabolism; there is greater dosage convenience resulting in better adherence to the treatment and less frequency of side effects, not to mention it allows prompt interruption of administration if necessary [3]. However, the stratum corneum allows penetration of only 1–5% of the substances applied topically, which reduces the efficacy of this route of application considerably. Lipophilic and small molecules (up to 500 Da) can pass through the stratum corneum because the keratinocytes are encased in a lipid matrix. Drugs that are hydrophilic and large are practically unable to penetrate intact normal skin, so

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passive topical delivery of drugs is limited [4]. The drug delivery technique seeks to optimize cutaneous penetration of drugs through chemical, mechanical, and physical methods, such as the addition of active permeators in the formulations used and the use of occlusion, iontophoresis, micro-needling, lasers, and intense pulsed light [2].

The use of drug delivery allows the penetration of the medication in the different skin layers: in the epidermis, locally in the dermis or transdermally, reaching the hypodermis, delivering the drug to the systemic circulation, a technique that has been gaining space in other medical areas. Therefore, the correct choice of technique and delivery depth of the drug is important, since many substances are not destined for the dermis, and the choice of product should be individualized for each case.

Skin Layers

The skin is a complex and dynamic organ, consisting of three main layers: epidermis; dermis, whose main function is to provide nutritional and structural support; and hypodermis, a reservoir of fat cells that plays an important role in body thermoregulation [5]. For the purpose of understanding the drug delivery process, the layer of interest in this chapter is the epidermis, more specifically the stratum corneum, which will be detailed below.

The Epidermis

The human epidermis is around 50 microns thick and its density is approximately 50,000 cells/mm^2. Its main constituent cells are keratinocytes, melanocytes, Merkel cells, and Langerhans cells [6]. Keratinocytes are found in a larger proportion, approximately 95%, and are arranged in a conformation described as "bricks and mortar": keratinocytes, composed of hydrated keratin, represent the "bricks," while the "mortar" is a bilipid layer consisting of ceramides, cholesterol, and fatty acids [6]. In the cell differentiation process, it takes 26–42 days for a basal keratinocyte to turn into a corneum and another 15 days for that cell to transit through the corneal layer and flake off. However, in some situations, such as in injured or inflamed skin, the rate of cell proliferation and maturation may be elevated to levels higher than those mentioned.

The skin barrier function is carried out by several components: the stratum corneum, the tight junctions, the microbiome, the chemical barrier, and the immunological barrier. When it comes to drug delivery and skin absorption, the mechanical barriers – the corneal layer and tight junctions – are the most important. However, other barriers also affect the microenvironment and can interact with active substances and carriers and therefore should be taken into account [7].

Just below the stratum corneum, the other layers of the epidermis (lucid, prickly, granular, and basal layers) make up the so-called viable epidermis, composed of 90% water, and are, therefore, of high hydrophilicity.

The Stratum Corneum

The stratum corneum, composed of flattened keratinocytes, densely arranged in terminal differentiation, anucleated and joined together by an extracellular lipid matrix, is the major limiting factor for the penetration of active substances applied to the skin. In addition, in certain dermatoses, such as actinic keratoses, the stratum corneum may be thickened and increase up to ten times its thickness, further limiting delivery of the drug applied to the skin [5].

The lipid-rich conformation of the stratum corneum leaves it with a hydrophobic character [8]. Lamellar bodies, formed during the keratinocyte differentiation, are essential in the delivery of lipids from the cells of the granulosa layer to the extracellular spaces of the stratum corneum [8]. The corneodesmosomes, other structures important in maintaining the structure of the stratum corneum, are located in the bilipid layer, and their function is to join the keratinocytes together and to maintain their size, shape, and cell grouping. The desquamation of the most superficial keratinocytes in the stratum corneum, which occurs regularly every 14 days, results from the disintegration of the corneodesmosomes by proteolytic enzymes [5].

In case of breakage of the permeability barrier, either by mechanical removal of the stratum corneum, topical solvent, or lipid extraction induced by detergent substances, it is the rapid secretion of preformed lamellar body contents – mainly regulated by concentration changes in calcium, potassium, and other ions – which initiates the homeostatic repair response rapidly recovering the barrier function [8].

In addition to lipids, organized in lamellar bilayers, the stratum corneum has enzymes, structural proteins, and microbial peptides that contribute to the barrier function, and it is considered metabolically active, changing both in structure and function along the path to the surface [9].

The influence of water on the stratum corneum is still debated. It is the extracellular compartment, in its outermost part, and not the cellular one, which presents greater alteration in response to the changes in the hydration [9]. It is known that many extracellular proteins, potentially bound to water, are present in the extracellular matrix. Some are secreted by the lamellar bodies, and others are the result of the degradation of the corneodesmosomes. As the corneodesmosomes are degraded, there would be gaps, such as an aqueous pore, through which hydrophilic molecules would be able to pass through the extracellular matrix [9].

Because of these characteristics of the stratum corneum, the limited substances able to cross the stratum corneum are those with small molecules, with maximum molecular weight of 500 Da and lipophilicity [1].

The penetration of drugs through the intact stratum corneum occurs by diffusion and, to a lesser extent, through the cutaneous appendages, and can be performed by the intercellular, which is the main pathway, or intracellular pathway [2]. In the

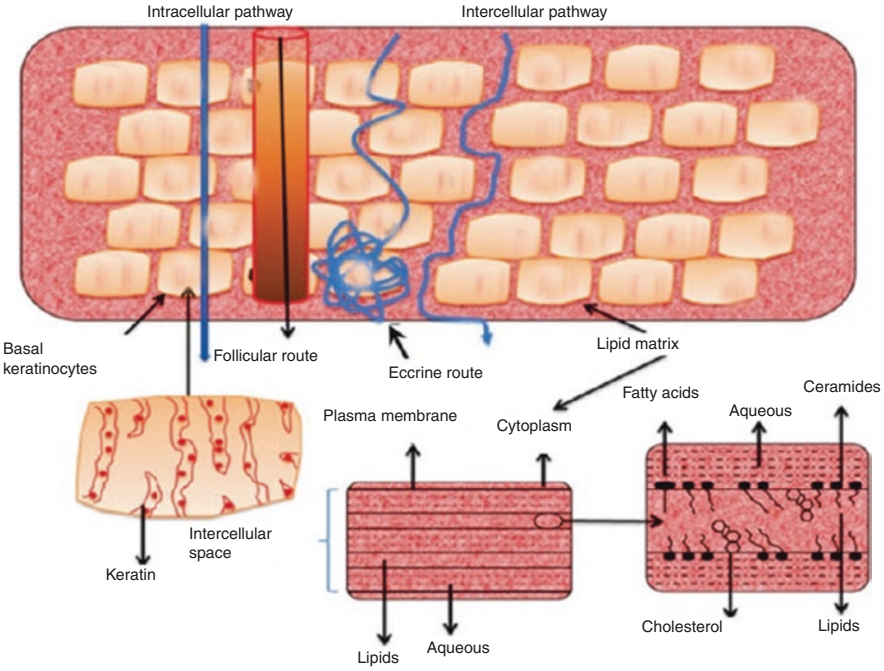

Fig. 1.1 Representation of the main routes for drug delivery and intracellular characteristics and the extracellular environment in the lower part of the figure. (Adapted from: Shahzad et al. [11])

intercellular pathway, permeation occurs around the corneocytes, so the larger the corneocytes, the greater the route for permeation. The size of the corneocytes varies according to the different areas of the body, and it is related to permeability.

Hydrophilic molecules can cross the stratum corneum through the intercellular pathway, since it is composed of aqueous areas surrounded by polar lipids that create the walls of channels that, in theory, can allow the passage of these molecules [10]. On the other hand, the intracellular pathway, though composed of water-rich keratinocytes, does not allow the permeation of hydrophilic active substances due to the lipophilic extracellular medium around it (Fig. 1.1) [11].

Microbiome

The skin is colonized by a variety of microorganisms, such as bacteria, fungi, parasites, and viruses; this set is called a cutaneous microbiome. Some of these organisms may be pathogenic, leading to cutaneous infections, while the commensal microbes prevent colonization and pathogenic infection by taking up space, consuming nutrients while producing bactericidal compounds. The microbiome also stimulates the adaptive immune system and enhances the host's innate immunity.

The proteins derived therefrom can result in the formation of a stable coating of nanoparticles, shielding them ("corona on nanoparticles"), which can alter the drug delivery [7].

Chemical Barrier

Microbial peptides are produced by keratinocytes and immune cells and are involved in the processes of protection, inflammation, and healing. They are effective against a wide range of microorganisms such as bacteria, fungi, and viruses [7].

Some of these peptides are permanently present on healthy skin, and their number may be increased in infections or skin lesions; others are produced only when induced. These peptides, as well as the proteins derived from the microbiome, can also cause the "screening" of nanoparticles [7].

The acid pH present on the skin surface also functions as a chemical barrier, since it decreases bacterial growth. It is altered in some diseases, such as in atopic dermatitis, and also affects the absorption of different substances applied on the skin [7].

Transepidermal Water Loss

Despite its barrier function, there is a constant evaporation of water through the stratum corneum, mainly coming from the underlying tissues and the sweat glands. Some situations, such as low temperatures and high relative humidity, decrease the evaporation rate, but even under such conditions water can still be lost by slow diffusion through the stratum corneum [12].

Transepidermal water loss (TEWL) represents the amount of water that is lost by diffusion through the skin surface, measured by the amount of water that evaporates on the skin surface [12]. TEWL measurements are routinely used in the pharmaceutical and cosmetic industry to assess skin irritation in response to the substances tested; advances in its measurement led to the use of TEWL to measure the barrier function of the stratum corneum [12].

Some situations in which there is disturbance of the skin barrier function show TEWL elevation, such as in patients with cutaneous xerosis and atopic dermatitis and after dermatological procedures that cause changes in the stratum corneum permeation. In addition, TEWL is affected by a number of factors: the anatomical area evaluated, skin and environmental temperature, and sweating [12].

Some studies have shown that the size of corneal stratum corneocytes and the number of stratum corneum cell layers lead to changes in cutaneous permeability and, consequently, TEWL: smaller corneocytes result in increased permeability since they favor the intercellular pathway. In addition, fewer corneocyte layers in the stratum corneum facilitate permeation as there are fewer cells to pass through

[13]. In this context, areas of thicker skin, such as the palmoplantar surface, are less permeable than the face skin, for example.

Tight Junctions

Tight junctions make the cell-to-cell junction and are responsible for restricting the passage of substances through intercellular space, acting not only as a physical barrier but also as a regulatory element [14]. They are composed of transmembrane proteins and protein plaques and are connected to the cytoskeleton of actin filaments.

Tight junctions are located in the granular layer and in the hair follicle; therefore they do not restrict the entry of active substances in the stratum corneum, but they limit the amount of active substances that will penetrate beyond the granular stratum [7].

For substances applied on healthy skin, they are the second mechanical barrier found in the interfollicular epidermis and in the upper part of the follicle; the horny layer is the first. In the middle and lower part of the hair follicle, they are the first barrier. Thus, the relevance of tight junctions as a barrier to drug delivery depends on how the drug will be delivered, whether through the stratum corneum or deep into the hair follicle. Diseases that progress with deficiency in the stratum corneum barrier function make tight junctions more accessible to topically applied drugs [7].

The TEWL maintenance function has been attributed to tight junctions, despite the loss of skin barrier function associated with aging. Although they are also damaged by ultraviolet radiation, tight junctions have good autoregenerative potential, with compensatory ability [14].

A better understanding of how these joints are modulated may allow their use – in combination with methods that facilitate passage through the stratum corneum – for a deeper delivery of the substances, as well as optimize their function in diseases with barrier function deficiency of the stratum corneum, where they become even more relevant.

Cutaneous Appendages as a Route for the Promotion of Drug Delivery

Although it occurs to a lesser extent, the permeation of active substances applied to the skin also occurs through the hair follicles. The stratum corneum close to the follicular opening is much thinner than the cutaneous surface, and there is a rich dermal vascularization underlying the follicle which would facilitate transporting the active substances that would penetrate through it [5]. However, the presence of sebaceous plug in the follicular ostium and of hair itself blocks the permeation of

active substances, limiting the use of this method [5]. Nevertheless, for ionic molecules and hydrophilic macromolecules, the transfollicular route is the main permeation pathway, since they cannot transpose the intact stratum corneum [15].

As an example of a method that uses the follicular route, we highlight iontophoresis. In this method electrical charges are used to drive drug molecules. Since cutaneous appendages show less electrical resistance, in this method of promoting drug delivery they contribute more effectively to the delivery of active substances [16].

Drug delivery methods that promote flaking and remove sebum and corneocytes from inactive follicles can also activate them and promote greater skin permeation of the substances applied to the skin [17]. Some authors suggest that the follicular route may be beneficial in diseases such as acne, alopecia, and folliculitis, which are related to cutaneous appendages [17].

The use of nanoparticles to optimize the follicular route has been studied, and there is evidence of greater penetration and longer residence time of the drug in the follicle with prolonged release (10 days with nanoparticles versus 4 days with traditional technology) using this technology [18].

Hydration and Skin Permeation

Some local skin factors have an effect on the permeation of drugs. The main one is cutaneous hydration: when well hydrated, the superficial corneocytes become swollen, and the intercellular lamellae become "disorganized," forming water-rich areas, which increases permeation of the stratum corneum [15]. Thus, methods such as occlusion, which promote hydration of the stratum corneum, increase skin permeation.

Transdermal Drug Delivery

For drugs/active substances whose final destination to effectively perform their function is the epidermis and dermis, the barriers to cross are smaller than the barriers to transdermal delivery, such as in the case of nicotine-containing patches and vaccines. In this situation, the drug should initially transpose the lipophilic stratum corneum, the aqueous portion of the epidermis, and finally the capillary vessels of the dermis, in order to be delivered systemically. That is why it is important that the substance to be transported has both lipophilic characteristics to cross the stratum corneum and hydrophilic characteristics to penetrate the viable epidermis toward the dermis successfully [3]. For transdermal delivery of active substances in the intact stratum corneum, only molecules <500 Da, with a melting point <200 ° C and whose required daily dose is less than 10 mg, can be effectively achieved.

How to Promote Drug Delivery

Strategies to promote drug delivery are diverse, ranging from the removal of the stratum corneum, the application of an electric gradient in order to carry molecules and facilitate their transport, to the opening of micropores in the epidermis [19]. Table 1.1 summarizes the main physical methods available to promote drug delivery and its proposed mechanisms of action. The technology used for drug delivery has been classified as an active or passive method. The increase of cutaneous permeability in the active method occurs through an external source of energy; conversely, in the passive method the increase of cutaneous permeability is based on the optimization of the formulation or the carrier vehicle [16].

The passive method has been advancing and showing modernization of the formulations used, aiming at increasing the driving force of drug diffusion and increasing permeability, such as the use of permeation enhancers, liposomes, and prodrugs;

Table 1.1 Main physical methods for promotion of drug delivery

Method	Method of operation	Mechanism of action
Electroporation	Micro-millisecond electrical pulses, high voltage (≥100 V)	Transient pore formation and disruption of cell membranes
Iontophoresis	Low voltage electric current (0.5 mA/cm^2)	It facilitates movement of ions through the cell membranes by the electrostatic effect, so that hydrophilic and charged molecules can be delivered
Lasers	Tissue ablation Photomechanical waves Non-ablative *resurfacing*	Heat removal of stratum corneum Light energy converted into mechanical energy Thermal injury and physical breakdown of the skin barrier
Microdermabrasion	Mechanical abrasion	Mechanical removal of stratum corneum
Micro-scrubbing	Micro-needles	Vertical microchannels that cause disruption of the skin barrier
External pressure	External mechanical pressure	External pressure
Radio frequency	High-frequency alternating current	Ionic cell vibration, heating, and tissue ablation
Sonophoresis	Ultrasound	Transient cavitation of intercellular lipids in the stratum corneum, thermal and mechanical effect
Magnetoporation	Magnetic field	Coupling of the drug to magnetic nanoparticles that will be attracted to the desired site through an external magnetic field
Thermoporation or microporation	Heat generated by metallic filaments, through electric impulse	Small openings in the stratum corneum

Source: Adapted from Haedersdal, et al. [19]

however, the amount of drug that can be absorbed using these methods is still limited since the barrier properties of the skin are not fundamentally changed [16].

Care

The rate of side effects and complications when drug delivery is used with proper care is low. In most techniques, at least part of the epidermis remains intact in the treated area, ensuring some degree of skin defense integrity.

It should be taken into account that the increased skin bioavailability of the substances used may increase the risk of complications, which is particularly important in the use of substances that may trigger inflammatory skin responses such as aminolevulinic acid, 5-fluoracil, and imiquimod.

Care should also be taken with the depth of drug delivery, whose safety profile is often evaluated only regarding topical use. Once it reaches the dermis, the substance may cease to act or minimize its effect on the surface and reach the vascular capillary system and may have systemic effects.

Concerning the risk of infection, the use of sterile products is questionable, since even with its use after correct antisepsis, contamination with cutaneous microorganisms may occur. Most of the studies used non-sterile products for drug delivery, and no complications or serious side effects were reported [20].

Conclusion

The topical route of drug delivery is essential in dermatology. For this reason, it is extremely important that the medication applied to the skin can penetrate and reach its target structure. By associating methods that promote drug delivery, it can be optimized.

Understanding the structure of the skin, the hydrophobic characteristics of the stratum corneum, and the main modalities available to promote drug delivery is essential for a comprehensive understanding of the technique and its correct application.

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Chapter 2
How to Optimize Drug Delivery in Dermatology?

Luiza Helena Urso Pitassi and Juliana Merherb Jordão

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

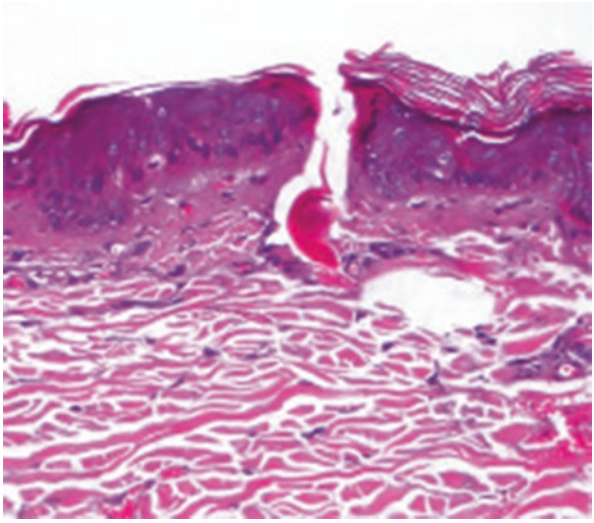

Fig. 2.1 Micro-channel created after the stratum corneum disruption, reaching the papillary dermis, with 1.5 mm microneedles. Histological section of swine skin stained by hematoxylin and eosin with a total increase of 40×. (Figure: Personal file Dr. Luiza Pitassi)

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].

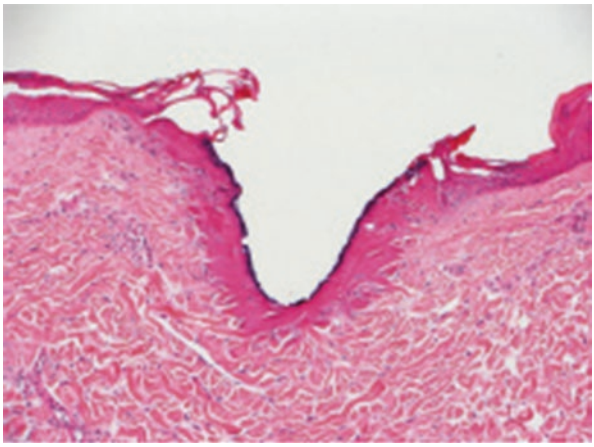

Fig. 2.2 Demonstration of the fractional ablative laser irradiated on the skin, forming micro-channels called microthermal zones (MTZ) that increase the hydrophilic and lipophilic substances permeability. (Figure: Personal file Dr. Luiza Pitassi)

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

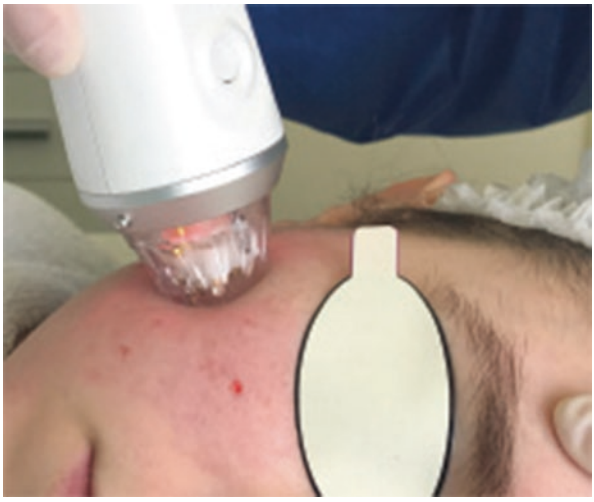

Fig. 2.3 Demonstration of the fractional microneedled radiofrequency application in the facial skin. (Figure: personal file Dr. Luiza Pitassi)

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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Chapter 3
Dermatological Applications of Drug Delivery Systems

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Abbreviations

ALA	5-aminolevulinic acid
CO_2	Carbon dioxide
EGF	Epidermal growth factor
Er: YAG	Erbium: yttrium-aluminum-garnet
FAL	Fractional ablative laser
IGF	Insulin growth factor
IPL	Intense pulsed light
MAL	Methyl-aminolevulinic acid
MMP®	Microinfusion of medication into the skin
MTZ	Microthermal zones
NAFL	Non-ablative lasers
NB-UVB	Narrow-band ultraviolet B
PCI	Percutaneous collagen induction
PDT	Photodynamic therapy
Q	Quality
RF	Radiofrequency
US	Ultrasound

Introduction

Effective topical drug delivery is crucial for the successful treatment of several dermatological conditions. However, the skin is a semipermeable barrier which limits the penetration of substances, so only 1–5% of these are absorbed and become

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Table 3.1 Dermatological applications of drug delivery systems

Skin rejuvenation
Scars
Melasma and post-inflammatory hyperpigmentation
Alopecia
Non-melanoma skin cancer and actinic keratosis
Vitiligo
Onychomycosis
Infantile hemangioma

bioavailable. Lipophilic drugs with a low molecular weight (≤500 Da) can passively diffuse through the skin. Advantages of topical administration include the avoidance of first-pass metabolism, sustained drug delivery, a reduced frequency of administration, and fewer side effects.

Topical drug delivery systems can temporarily increase skin permeability by creating microchannels which allow for enhanced transepidermal/transdermal penetration of topically applied substances, maximizing their effects. These techniques include iontophoresis, ablative fractional lasers (AFLs) and non-ablative fractional lasers (NAFLs), intense pulsed light (IPL), microneedling, fractional radiofrequency and ultrasound.

The main indications of topical drug delivery systems are listed in Table 3.1.

Intense Pulsed Light and Laser-Assisted Drug Delivery

The most widely used AFLs are 2940 nm *erbium: yttrium-aluminum-garnet* (Er: YAG) and 10600 nm carbon dioxide (CO_2), both of which are infrared water-targeting lasers. These lasers create vertical cylindrical microchannels of tissue damage surrounded by coagulation zones, known as microthermal zones (MTZs), as a result of thermal injury to the skin. MTZs, in turn, are surrounded by untreated tissue, facilitating tissue repair and preventing scarring.

NAFLs and IPL increase skin temperature, promoting the fluidification of lamellar lipid bilayers and increasing skin permeability, especially to lipophilic substances. Quality (Q)-switched lasers, in turn, produce ultrashort waves with high energy peaks which disrupt keratin filaments and corneocytes, forming micropores in the stratum corneum and increasing the surrounding temperature.

Indications for Intense Pulsed Light and Laser-Assisted Drug Delivery

Treatment of Non-melanoma Skin Cancer and Actinic Keratosis

The use of laser-assisted drug delivery in the treatment of non-melanoma skin cancers and actinic keratosis has been investigated by several studies. The substances most frequently involved in these investigations are 5-aminolevulinic acid (ALA),

methyl-aminolevulinic acid (MAL), imiquimod, 5-fluorouracil and ingenol mebutate.

Haedersdal et al., for instance, used a swine model to demonstrate the increased penetration of MAL in deep dermal layers after treatment with a fractional CO_2 laser. Cai et al. compared the use of a CO_2 laser alone or in combination with photodynamic therapy (PDT) and ALA in the treatment of Bowen's disease. The remission rate of lesions in the group treated with both techniques was 72.73% and the recurrence rate 9%. In a study by Ko et al., the combination of TFD-MAL and a 2940 nm Er: YAG laser was significantly more effective in the treatment of actinic keratosis of the face when compared to TFD-MAL alone. The combined treatment was also associated with lower recurrence rates.

Nguyen et al. showed a histological cure rate of 87% in patients with superficial basal cell carcinoma and spinocellular carcinoma in situ after CO_2 laser-assisted topical treatment with 5% 5-fluorouracil. Mild local adverse events such as erythema and erosion were reported.

Braun et al. showed that pretreatment with an Er: YAG laser followed by the application of 0.015% ingenol mebutate led to improved results in the treatment of field cancerization. The temporary opening of the epidermal barrier generated by the AFL allowed for increased drug penetration into deeper layers of the skin, increasing bioavailability.

Vitiligo

Studies have reported success in the treatment of vitiligo with corticosteroids and 5-fluorouracil associated with narrow-band ultraviolet B (NB-UVB) phototherapy and AFLs to enhance drug delivery. In a study by Li et al., the use of betamethasone in addition to CO_2 laser treatment and NB-UVB phototherapy led to significant improvements in repigmentation. In a case report by Kalil et al., a patient with vitiligo also showed an excellent response to three sessions of CO_2 laser treatment and desonide.

Scars

Hypertrophic scars and keloids are often treated with corticosteroid injections, but this can cause undesirable adverse events such as skin atrophy. Waibel et al. observed positive effects such as improvements in hypertrophy, texture, and dyschromia after three to four sessions of fractional CO_2 laser treatment followed by topical applications of triamcinolone acetonide. Kalil et al. reported on a patient who experienced positive outcomes in the treatment of keloids after a single session of 2940 nm Er: YAG laser treatment followed by triamcinolone. A separate patient showed improvements in perioral scarring after six sessions of 1340 nm Er: YAG laser treatment associated with insulin growth factor (IGF) and epidermal growth factor (EGF) administrations.

Alopecia

Kalil et al. reported excellent results in the treatment of androgenetic alopecia with 1340 nm Er: YAG laser-assisted drug delivery of minoxidil. The same authors also reported on a patient with a single patch of alopecia areata who showed an excellent response to 2940 nm Er: YAG laser treatment followed by the application of growth factors. Issa et al. described two patients with alopecia areata who achieved full recovery after a session of CO_2 and ultrasound-assisted drug delivery of triamcinolone.

Skin Rejuvenation

The number of studies involving medication to promote skin rejuvenation has increased significantly over recent years. Waibel et al. conducted a split-face study to evaluate the effects of fractional CO_2 laser-assisted delivery of a solution containing 15% vitamin C, 1% vitamin E, and 0.5% ferulic acid. The portion of the face which received this treatment showed accelerated healing, with an increased concentration of fibroblast growth factors observed in the molecular analysis of biopsy material, although split-face comparisons were not statistically significant. Hsiao et al. showed a significant increase in the skin permeation of vitamin C after treatment with ablative fractional Er: YAG and CO_2 *lasers*.

Melasma and Post-inflammatory Hyperpigmentation

Laser toning is a technique where a low-frequency Q-switched 1064 nm Nd: YAG laser beam is moved several times over the area of interest in order to stimulate neocollagenesis. This method can also be used in combination with medication. The combined effects of laser toning and topical vitamin C in the treatment of melasma were examined by Lee et al., in 2015. The authors found that the treatment led to significant improvements in facial pigmentation.

Onychomycosis

Topical antifungal treatments for onychomycosis are usually ineffective, since these drugs have difficulty penetrating the nail plate. Many patients have contraindications to systemic treatments due to medical comorbidities and the risk of adverse effects or drug interactions. AFL-assisted drug delivery has emerged as a promising alternative for these populations. The lasers create columns of ablation, removing the affected nail tissue and facilitating the penetration of medication. Bhatta et al. obtained positive results in the treatment of onychomycosis using a combination of CO_2 laser treatment and terbinafine cream. The substances most commonly used in this type of study are terbinafine, luliconazole, and amorolfine creams.

Infantile Hemangioma

Ma et al. evaluated the efficacy of CO_2 laser-assisted timolol delivery in 1- to 6-month-old infants with deep infantile hemangioma. The patients exhibited clinically significant improvements, with moderate to excellent hemangioma activity scores. No complications or side effects were observed in the study.

Microneedle-Based Drug Delivery

Microneedling, also known as percutaneous collagen induction (PCI) therapy, involves the creation of several micropunctures in the skin, resulting in an inflammatory stimulus which triggers increased collagen production. This is done using a polyethylene roller equipped with sterile stainless steel microneedles. Applications of this technique range from the treatment of scars and blemishes to skin rejuvenation, alopecia, and even the enhanced penetration of topically applied substances. Microneedle arrays are also an effective method to enhance drug delivery. The disruption of the skin barrier by the microneedles prompts the release of cytokines, followed by dermal vasodilation and the migration of keratinocytes. The healing process begins with the synthesis of type III collagen, which is later replaced by type I collagen, producing rejuvenating effects on the skin and improving the appearance of scars. This technique promotes collagen production without the de-epithelization caused by ablative techniques.

The needles must be at least 1.5 mm long in order to reach the dermis and promote collagen remodeling. These tiny wounds in the papillary dermis result in superficial bleeding and the release of several growth factors that stimulate fibroblast proliferation and collagen synthesis. Microneedling therefore induces neocollagenesis and neoangiogenesis, initiating a tissue remodeling process that continues for months after the procedure. The use of microneedles allows for drugs to be introduced in the channels created in the stratum corneum, allowing for direct delivery to the vascularized upper dermis. The increase in skin permeability persists for 48 h after microneedling is performed. This procedure has a short recovery time and can be used in patients with darker skin phototypes with a lower risk of adverse effects, such as post-inflammatory dyschromia, relative to other techniques. Microneedling should therefore be considered a valuable treatment option, especially for patients with darker skin phototypes, since this method is associated with a lower likelihood of adverse effects than other procedures that injure the epidermis.

Contraindications include active acne, labial herpes, or other local infections; moderate to severe chronic skin disease such as eczema and psoriasis; blood dyscrasias; concurrent anticoagulant therapy; strong tendency to keloid formation; and current chemotherapy or radiotherapy.

Indications of Microneedle-Assisted Drug Delivery

Acne Scars

The most frequent indication for microneedling is the treatment of acne scars. Microneedling improves skin texture and has a discreet effect on acne scars according to Kalil et al., who examined the effects of topical application of growth factors after microneedling as a treatment for acne scars. Ice pick scars, however, did not improve after treatment, corroborating the finding of previous studies. According to Lima et al., the use of microneedling after chemical peeling with 88% phenol produces better outcomes in the treatment of skin laxity, fine lines, and depressed acne scars than either method alone, making for a promising addition to the treatment arsenal for these conditions

A study conducted by Chawla found that microneedling combined with platelet-rich plasma led to an excellent treatment response, producing better results than those obtained with the use of vitamin C. However, it is important to note that the results of both treatments were considered satisfactory. The efficacy of chemical peeling with 35% glycolic acid combined with microneedling has also led to positive cosmetic outcomes in the treatment of acne scars when compared to either technique alone, as reported by Sharad.

Other Scars

This technique can also be used to improve the appearance of hypertrophic scars, burn scars, stretch marks, and other atrophic scars. According to a study by Aust et al., the topical application of vitamins A and C followed by microneedling to maximize collagen induction led to significant improvement in the appearance of burn scars. Histopathological analysis revealed an increase in collagen and elastin deposition 12 months after the procedure.

Dyschromia

A recent review published by Hou et al. revealed that topical tranexamic acid followed by microneedling led to larger clinical improvements in the treatment of melasma as compared to the use of tranexamic acid microinjections alone. Microneedle-based delivery of a whitening cream containing kojic acid has also proved effective in the treatment of periorbital hyperpigmentation. The effectiveness of this technique in the treatment of vitiligo, however, is still unknown.

Skin Rejuvenation

Percutaneous collagen induction improves skin appearance by reducing fine lines, wrinkles, and pores and maintaining skin flexibility and elasticity. Topical treatments used in combination with this technique include vitamin C and tretinoin.

Microneedle-based drug delivery systems can also be used to improve skin texture on the face, hands, and stretch marks, yielding positive results due to the increased permeability of the stratum corneum. A study conducted by Kalil et al. found that this set of techniques produced satisfactory results in the rejuvenation of skin in the anterior thorax, with good tolerability, minimal adverse effects, and high patient satisfaction. The study concluded that microneedling may be a safer and less invasive alternative to AFL for the treatment of the anterior thorax. The study also showed that the use of formulations during and after the procedure increased its effectiveness and minimized the likelihood of adverse events, including pigment alterations.

Alopecia

Recent studies have revealed the superior efficacy of microneedle-assisted drug delivery and minoxidil in the treatment of androgenetic alopecia relative to topical treatment alone. In a study conducted by Dhurat et al., the hair count of patients treated with both techniques increased by approximately 80%, while those who received topical treatment only showed no significant improvements over time. Microneedling induces the release of platelet-derived and epidermal growth factors, activating stem cells in the hair follicle bulge and resulting in the overexpression of hair growth-related genes. In light of these findings, this technique was recently introduced as a treatment option for androgenetic alopecia. Another recent technique, known as microinfusion of medication into the skin (MMP®), relies on microneedle-assisted drug delivery using tattoo machines and needles. Additional studies are still needed to demonstrate the superiority of combined minoxidil injections and microneedling over topical minoxidil, microneedling alone, and the MMP® technique.

The combination of microneedling and topical corticosteroids has also emerged as a promising treatment for alopecia areata. However, these techniques have only been tested in small samples, and further studies are required to evaluate treatment responses in the long term.

Actinic Keratosis

Microneedling can be used as a complement to photodynamic therapy (PDT) in the treatment of actinic keratosis and photodamage. Clinical trials performed by Kassuga et al. evaluated the use of these techniques in combination with transepidermal methyl-aminolevulinate (MAL) delivery through fractional radiofrequency and ultrasound in the treatment of multiple actinic keratoses. This method had greater efficacy and better outcomes than standard PDT. However, this approach to PDT must still be examined in future studies.

The combination of fractional radiofrequency (RF) and ultrasound (US) has a twofold effect: the fractional RF opens up microscopic channels in the skin, while the low-frequency US waves propel the drug molecules through these channels. This method can increase the penetration of hydrophilic substances and macromolecules in the dermis, facilitating transepidermal delivery.

Microneedle Radiofrequency

This method creates thermal zones without epidermal damage, promoting dermal remodeling and new collagen deposition. It can be used to treat acne scars as well as active acne lesions, as described in a recent review conducted by Hou et al. Microneedle radiofrequency can treat active acne lesions by interfering with sebaceous gland activity, reducing sebum production and keratinocyte hyperproliferation.

According to Kim and colleagues, this technique can also be targeted at sweat glands in order to treat hyperhidrosis. This claim was supported by reductions in the number and size of apocrine and eccrine glands observed in biopsies performed one month after the end of treatment.

Ultrasound

The use of US in drug delivery is known as sonophoresis or phonophoresis. Skin permeability can be increased by low-frequency US, via acoustic cavitation above the skin, or high-frequency US, by cavitation inside the skin, which is the most widely used method for this purpose. Both techniques can also be used to maximize drug absorption.

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Chapter 4
Drug Delivery-Associated Dermatological Technologies and Techniques

Abdo Salomão Júnior and Gustavo Bastos Salomão

Introduction

Medicine is a tireless science in the search for new drugs and therapeutic options for health and longevity benefits. Dermatology is one of the specialties that have evolved the most in this direction, especially with regard to the development of innovative and creative technologies, which have allowed us to deal with most of the complaints of patients.

The skin is the largest organ in the body, making up about 16% of body mass. It is structured into two primary layers, epidermis and dermis, which are composed of epithelial, mesenchymal, glandular, and neurovascular components. Among the various skin functions, the main one is that of coating and protection [1].

The epidermis, of ectodermal origin, consists of the outermost layer of the skin, being the body's point of contact with the environment. The biological and physical characteristics provide a relevant role in protecting against aggressive environmental factors, infectious pathogens, and chemical substances [2]. The epidermis is organized into functional layers, defined mainly by the characteristics of keratinocytes (such as size, shape, nucleation, and expression of keratin). These layers are stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum (outermost layer) [3].

Epidermal keratinocytes, originating from cell division of stem cells in the stratum basale, as they migrate toward the skin surface to form corneocytes, undergo several differentiation processes, which involve enucleation and keratin

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accumulation [4]. Keratinocytes also receive melanin from melanocytes [5]. Corneocytes are dead but intact cells, strongly linked together by desmosomes and communicating junctions to form the outermost barrier of the epidermis, the stratum corneum [3].

The stratum corneum contains about 10 to 25 layers of corneocytes, being composed of proteins (79–90%) and lipids (5–15%). It is flexible, but relatively impermeable, consisting of the main obstacle to the cutaneous penetration of drugs [Marwah et al. 2016]. Thus, the main barrier for skin permeation of drugs is precisely the stratum corneum.

The possibility of addressing skin problems locally has been the subject of attention for decades. For such, it is necessary to cross the skin barrier in a practical, safe, and controlled manner, enabling local action of drugs without systemic and hepatic circulation, thus making the assets available directly where desired. In this context, transdermal drug delivery systems are promising alternatives to increase local and systemic efficacy of drugs, including anticancer agents [7].

The transdermal route of administration has several advantages compared to oral and intravenous routes, the main ones being delivery of the drug directly to the target tissue without the first pass effect through the liver, resulting in increased efficacy and reduced toxicity [6].

The main limitation of this technique is that only low molecular weight drugs (a few hundred Dalton's) have good penetration, which is the main difficulty in permeating hydrophilic molecules, macromolecules, and peptides [6].

Systems Used for Drug Delivery

Skin Microneedling

Microneedling has the purpose of breaking the integrity of the skin barrier, allowing communication between the external environment and deeper layers of the skin, through which substances that are normally unable to cross can pass.

The advantages of microneedling were first observed by Andre Camirand, MD., in the 1990s, when he performed camouflage tattoos on his patients' hypertrophic scars to disguise the unsightly appearance. After a year or two, patients returned without pigmentation and with an important improvement in texture, color, and appearance of scars. The experience gave him the idea of needling hypertrophic scars with a dry tattoo machine (without ink), which he did successfully.

In 1996, Desmond Fernandes, another researcher, presented at the ISAPS Congress in Taipei the results of needling upper lip hair with a device similar to a needle stamp created by him. From there, new ideas and devices have emerged and have shown very promising results.

Nappage

Nappage is a variant of mesotherapy created in France by Michel Pistor in 1958, and it was, perhaps, one of the first forms of microneedling with drug delivery for skin improvement. It was widely used in the 1990s, after which it was replaced by more modern technologies, such as lasers and rollers.

The technique consists of making numerous superficial and contiguous punctures on the skin while applying pressure to the syringe's plunger, allowing drops of the drug mixture to flow out. A certain skill is required to make holes more superficially with homogeneous coverage of the entire skin.

Punctures should be delicate, but deep enough to cause bloody dew, which brings growth factors that will assist in the repair of injured epidermis. The correct technique is not to inject but only to puncture and let the drug diffuse.

After the procedure, the skin may be swollen and erythematous for 2–3 days, being necessary to avoid the sun until complete recovery.

Despite being a superficial treatment, it is advisable to use anesthetic cream, which must be removed with saline solution before the procedure. We did not find scientific papers indexed on the technique.

Rollers

These are portable devices, cylindrical solids with rotating surfaces encrusted with metallic needles and arranged in parallel and equidistant lines, with support cable for handling the applicator. Needle sizes can vary between 0.2 mm and 2.5 cm.

Needle reach:

- 0.25 mm – stratum corneum
- 0.5 mm to 1 mm – epidermis
- 1.50 mm to 2,5 mm – dermis

The first roller appeared in 2004, and since then, new and different types, sizes, and qualities are available on the market, from high performance devices for medical use to products of dubious origin, sold without criteria over the Internet, for home use or in aesthetics clinics.

The roller for medical use must be sterile, of proven quality and origin, manufactured with sturdy stainless steel surgical needles. There are many imported brands being marketed in Brazil, and it is always necessary to investigate whether the equipment is approved for use in our country *(Law #6437, of August 20, 1977, published in the DOU of August 24, 1977 - Buying products without ANVISA is a CRIME. The doctor can answer for a crime against public health; up to 15 years of sentence (Articles 273 and 344 CP)).*

The roller must be applied evenly in several directions in order to treat the entire surface of the skin, promoting controlled injuries and bleeding equal to or greater than a bloody dew. The greater the number of movements, the better the result, however, the greater the risk, discomfort, bleeding, and downtime.

Fig. 4.1 Schematic drawing of a roller for medical use

Microneedling alone already improves and rejuvenates the skin, by activating healing mechanisms and stimulating collagen. Bleeding contributes to the migration and action of growth factors at the site (Fig. 4.1).

Treatment effectiveness depends on several factors, such as size of needles, number of movements, application strength, homogeneity of application, patient compliance, skin quality, age, skin thickness, sun damage, vascular changes, and number of sessions.

Regarding the transdermal passage of drugs, it is not possible to say whether it occurs or not, how much of it actually occurs, and how deep. Microneedling is not a good method for transdermal drug infusion.

Microinfusion of Drugs into the Skin (MMP®)

MMP® is a technique that uses tattoo machines for microneedling and concomitant drug delivery. The idea came up in 2011, at a meeting of tattoo artists, from the observation of the machinery's functioning mechanism and its mode of action on the skin.

Assuming that the tattoo is the result of controlled microneedling, the perforations of which are filled with pigments that are fixed and remain where they are placed, the possibility of changing the ink for a drug and using the machine for skin treatments was considered.

MMP® differs from dermopigmentation in one main point: the infused active ingredients do not remain in place indefinitely like pigments in paints. They are absorbed and eliminated after a variable period of time. The drugs used must be for intravenous or intradermal use and are chosen according to the pathology to be treated.

Cartridges (disposable part of the equipment) are sterile, for single use. There are more than 50 types of cartridges with varying spatial needle configurations (Fig. 4.2).

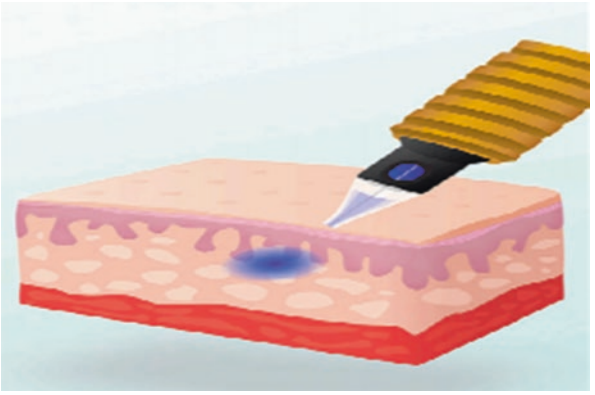

Fig. 4.2 Schematic drawing showing the MMP® technique. (Source: Samir Arbache, MD)

Fig. 4.3 Schematic drawing of Dermapen®

Topical anesthetics are used on the face, and, if necessary, blockages or infiltrative anesthesia can be used on the scalp.

In research on MMP®, we found a paper published in the *Journal of the American Academy of Dermatology* on the treatment of idiopathic guttate hypomelanosis using 5-fluorouracil [8].

Microneedling by Pens (Dermapen®)

They are electric and vibrating devices of microneedling, in the shape of a pen, where a disposable tip is attached, generally composed of 12 needles arranged in a circle, which move vertically toward the skin, piercing it intermittently (Fig. 4.3).

The height of the needles is adjustable, as well as the speed of movement, allowing more superficial or deeper treatments to be performed on the same patient, according to the need.

Treatment requires topical anesthesia to reduce possible discomfort and has the same indications and contraindications as rollers.

We did not find any indexed scientific papers related to the device.

Fractional Radio Frequency

The medical use of radio frequency (RF) began in 1978 when Manes and colleagues defined the ideal frequency for cutting and coagulating an alternating current. This frequency is in the FM radio band, which is why it is called radio frequency.

High frequency causes positive and negative charges to oscillate within the cells, raising the temperature quickly, which can generate heat, clotting, and sometimes even vaporization of the tissues. In general, the smaller the spot, the greater the vaporization, as the energy is more concentrated.

According to the waveform used, a type of biological effect is generated in the tissues. If the current is of the braked type, the effect will be coagulation. If the current is pure sinusoidal, it will be cut. Moreover, if it is sinusoidal, it will be cut with coagulation.

In the last few years, the use of RF has been extended far beyond the surgical function. Following the tendency of lasers to fractionate energy to offer safer treatments and with less downtime, fractional radio frequency emerged, with a different operation from common RF; it was indicated for rejuvenation treatments, acne scars, stretch marks, open pores, and several other dermatological indications.

Fractioning was possible by introducing multi-needle tips coupled to pulsed electrodes (in place of balls and arcs). The configuration of the new tips allows treating a part of the skin and sparing the neighboring region, from which the injured portion is recovered, as in a fractional laser.

This technology concentrates the RF energy in small point electrodes, producing columns of ablation and coagulation in the epidermis and dermis depending on the energy used, without reaching the subcutaneous tissue. This process creates several micro-channels, referred to as microscopic treatment zones. Through such micro-channels, several molecules can pass toward the deeper layers of the skin [9].

Fractional RF is bipolar, with the negative centrifugal pole attracting electrons and causing the coagulated tissue columns to be thicker in depth than on the surface. In this way, most of the surface area of the skin remains intact and untreated. This region functions as a reservoir of stem cells, growth factors, and inflammatory cells, which are able to quickly migrate to traumatized skin and facilitate healing [9].

Treatment causes a change in skin barrier, which becomes shortly more permeable and can be used to perform a drug delivery with the necessary actives.

Iontophoresis

It is a technique for therapeutic purposes, developed from physical-chemical concepts that seek to increase the penetration of ionic agents into the skin, using a low-frequency continuous electric current.

The method was initially described by Pivati in 1747, with further studies and advances. At the end of the nineteenth century, Morton, in his book on ion

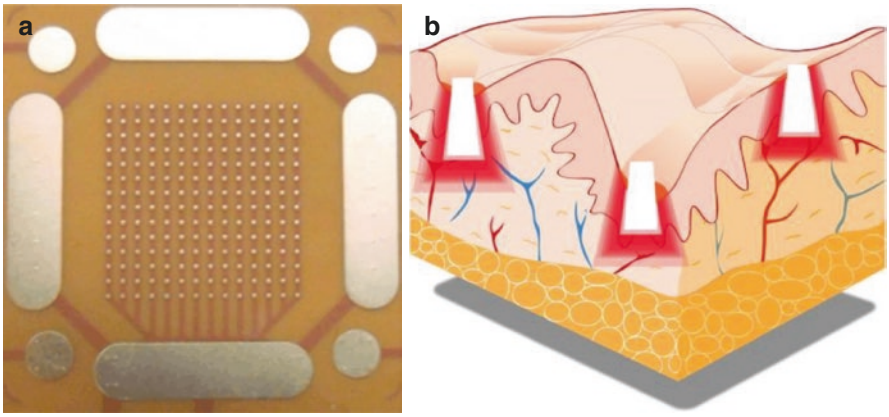

Fig. 4.4 Fractional RF. (**a**) Image of the electrode; (**b**) Schematic representation of the skin

cataphoresis, reported an experiment in which he deposited powdered graphite on his own arm and applied a positive electric current through it, resulting in the appearance of black spots on the skin that persisted for several weeks, proving the permeation of graphite (Fig. 4.4).

It was only at the beginning of the twentieth century that the technique became more known, based on the work of Le Duc, who described the fundamentals of the method and its applicability in medicine.

Curdy C. and Kalia YN also contributed, more recently (2000, 2001, and 2002) with important researches (permeation of piroxicam) that prove the validity of the technique.

Iontophoresis devices use electrical concepts of polarity (attraction and repulsion) and work with continuous low-frequency current whose electrons always travel in the same direction.

They have two types of electrodes: a neutral, called passive, and another active, with variable polarity, that has to be chosen according to the need (positive or negative). The charge of the active electrode must always coincide with the charge of the drug, generating a continuous repulsion of the ion and facilitating its entry into the skin, through the pores, ducts of sweat, sebaceous glands, and crevices of the broken stratum corneum. It is the electro-repulsion mechanism.

Another mechanism involved in iontophoresis is electro-osmosis: the passage of the current causes a flow of water from the positive pole (anode) to the negative pole (cathode) which causes a transdermal movement of ionizable substances. Normally the skin tends to get acidic (pH 3 to 4), and keratin in the stratum corneum is electrically neutral. Under these conditions, electro-osmotic flow increases the penetration of negative ions, while the release of positive ions is delayed.

It is not yet clear which mechanism plays a major transfer role in iontophoresis – electro-repulsion or electro-osmosis.

The amount of ions introduced by iontophoresis through the skin follows Faraday's law, and it is possible to state that the longer the application time and

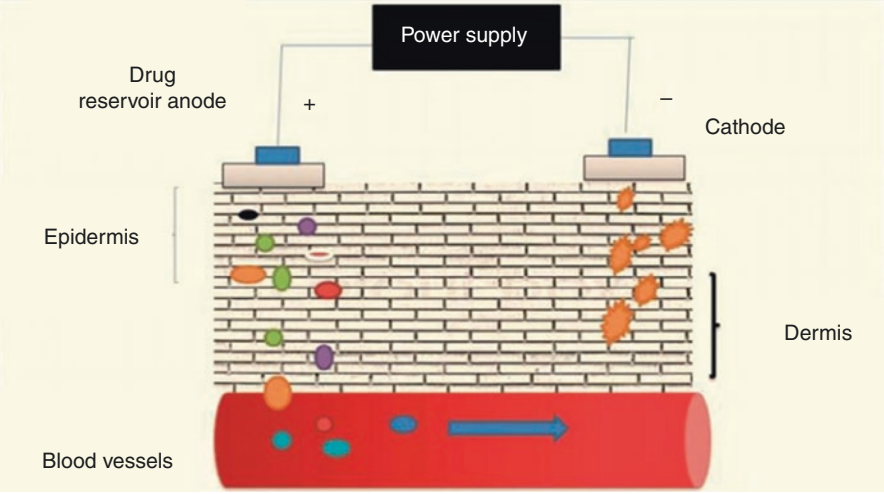

Fig. 4.5 Iontophoresis technique. (Adapted from Marwah et al., 2016)

current amplitude, the greater the amount of ions transferred. It is also possible to deduce that the smaller the current amplitude, the longer the application time necessary for the same amount of ions to be transferred, or vice versa. There is a maximum amplitude that can be worked on, which can be determined by the current density. The amplitude/time ratio suggested by the Food and Drugs Administration (FDA) is 80 mA/min.

The size of the electrode must be compatible with the target area, and eventually, the doses calculated by the current density can reach values that can cause burns or local irritation by stimulating free nerve endings.

Thus, it can be said that iontophoresis is an alternative to enhance the transfer of ionizable substances through the skin, reaching concentration levels higher than passive diffusion not facilitated by electric current, thus allowing desirable therapeutic levels. However, it is not a simple and practical technique, as it suffers interference from numerous factors that hinder the process and certainly needs more in-depth knowledge of physical-chemical concepts (Fig. 4.5).

Phonophoresis

Phonophoresis or ultrasonophoresis is the use of ultrasound on the skin combined with a pharmacological gel (added with active ingredients of interest to the local treatment), with ultrasonic waves acting as a permeation facilitating agent.

Ultrasound therapy is widely used in physiotherapy to treat diseases and injuries of soft tissues. Various types of drugs, such as corticosteroids and anti-inflammatory

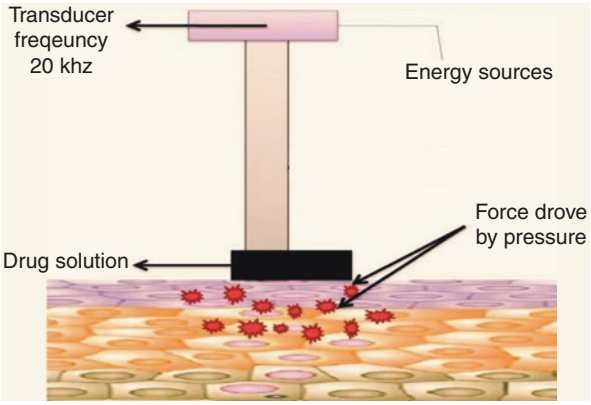

Fig. 4.6 Ultrasound technique. (Adapted from Marwah et al. 2016)

drugs, have been added to a gel base (used as a coupling medium) and administered through this route.

The waves can be applied in two ways: in continuous form (50% thermal effect and 50% mechanical effect) or in intermittent form (100% mechanical, pulsatile, athermic) (Fig. 4.6).

The lack of interest in the technique in dermatology is probably due to the difficulty of obtaining actives resistant to denaturation of the waves of the device.

Electroporation

Electroporation consists of the application of ultra-short electrical pulses (microseconds or milliseconds) of high voltage, which increase the membrane transport potential by promoting a transient formation of aqueous pores in the lipid layer of the stratum corneum, allowing macromolecules to migrate through these pores.

The effectiveness of the transport depends on the physical and chemical properties of drugs and electrical parameters used, such as pulse frequency, waveform, and intensity of the electric field.

The high voltage pulse is well tolerated but can trigger uncomfortable muscle contractions. The method was more popular in the 1980s, with the publication of in vitro studies, and in the 1990s, with in vivo studies.

Electroporation equipment works with two types of electric waves:

- The exponential decreasing wave, of milliseconds, which causes disorganization in the dual lipid layers of the stratum corneum and brief failure in the "barrier" function, as well as transient increase in blood flow. It has advantages because it maintains the state of high permeability but depends on the resistance of the skin and the system used (electrodes, conduction media).
- The square wave, constant and less than 100 milliseconds in duration, changes the impedance of the skin and increases the loss of transepidermal water.

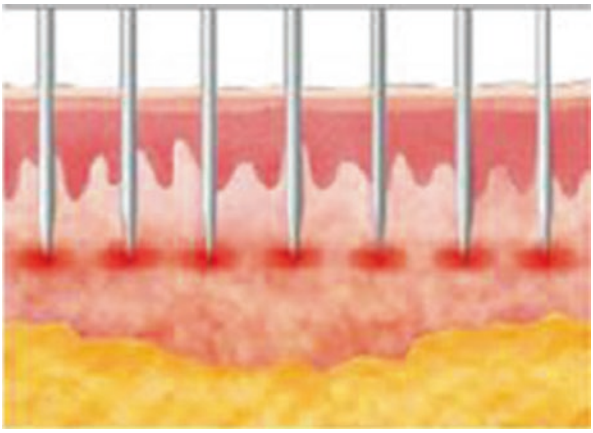

Fig. 4.7 RF with microneedling. Schematic representation of the microneedling RF system with isolated needles making clotting points in the dermis

Some researchers have reported the use of electroporation in cancer patients to permeate impermeable cytotoxic drugs such as bleomycin and cisalpine, in tumor cells (electrochemotherapy), with more effective effects than chemotherapy alone.

The use of the method in aesthetic dermatology still lacks scientific studies that prove its applicability. Some studies show that the methods of iontophoresis, phonophoresis, and electroporation can be used together in the same patient, enhancing the desired permeation effects. However, as has already been said, these are methods in which the knowledge of physics, chemistry, and electricity is essential for a full understanding of how the techniques work (Fig. 4.7).

Microneedling with Radio Frequency

Microneedling RF represents a new modality of micro-invasive treatments. Gold-plated microneedles penetrate to predetermined depths in the epidermis, dermis, or even hypodermis. There are different types of microneedles, that is, isolated, emitting electrons only at the tips, or not isolated, emitting electrons across the length of the stem. As for polarity, they are always bipolar and there may be alternation of polarity [10].

The expected beneficial effects of RFMA are due to several factors: the delivery of actives directly to the expected location, the denaturation of skin proteins by heat of electromagnetic waves, the contraction of collagen fibers, the activation of fibroblasts, and consequent neocollagenesis (Fig. 4.8).

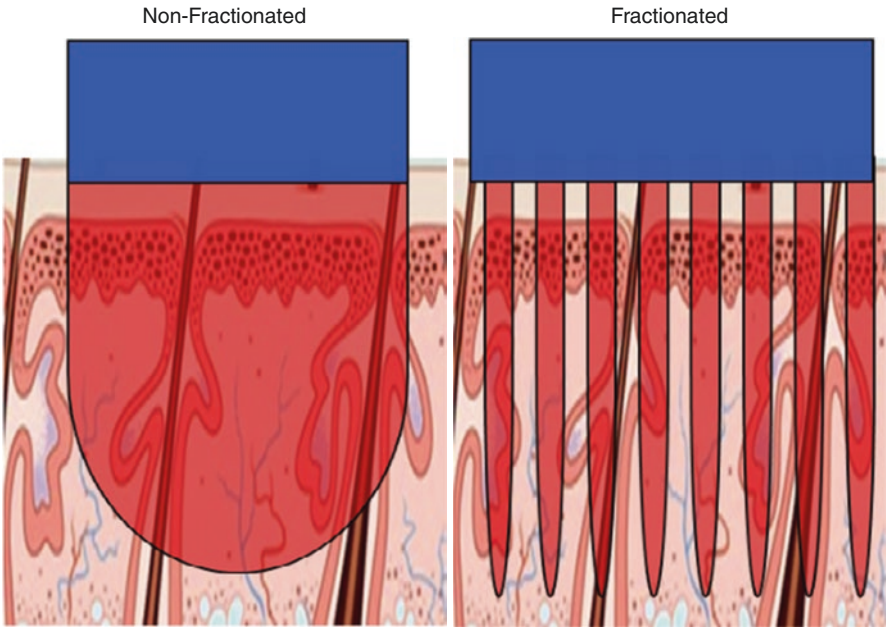

Fig. 4.8 Schematic drawing comparing non-fractionated and fractionated lasers

Ablative Fractional Laser

Thermal ablation devices selectively heat the skin's surface in a fractionated way, generating micro-perforations in the stratum corneum.

The surface becomes temporarily heated to more than 100 degrees in fractions of a second, without allowing heat to spread to neighboring tissues [Prausnitz MR. et al. 2008]. Thermal ablation involves the vaporization of water from the stratum corneum resulting in micro-craters on the skin surface.

At the central point of each radius, the tissues vaporize at high temperatures (ablation). Right after that, a thin layer of carbonization can sometimes be absent, more externally and adjacent a coagulation layer and, even more externally, an extensive area of hyperthermia. The proportion of each layer depends on the pattern generated by each wavelength of each laser. In this way, CO_2 laser (10.600 nm) generates a coagulation layer much larger than the erbium-yag (2.940 nm).

More recent studies suggest that temperatures well above the boiling point of water are necessary and that other processes, such as tissue combustion, are also involved.

Of the ablative fractional lasers, CO_2 has shown a better performance for the delivery of dermatological actives, since the remaining coagulation column works as a reservoir of actives, slowly releasing them, generating more lasting and homogeneous results (Figs. 4.9 and 4.10).

The main negative points of drug delivery by CO_2 laser are long downtime, very painful procedure, and high rates of side effects.

Injection Microneedles

An effective and safe transdermal infusion must be based on achieving a balance between the effective delivery of drugs and the safety of the procedure. Some third-generation systems have been well tolerated for this purpose, especially systems that use injector microneedles and thermal ablation [11].

D&D is a device developed for transcutaneous delivery of pharmacological actives, dermocosmetics, or health products, in predetermined places, which can be in the epidermis, in the dermis, or even in the subcutaneous cellular tissue.

This delivery to predetermined locations avoids the massive systemic circulation of drugs for the purpose of dermatological use, that is, to treat the skin, it will not be necessary to circulate the drug throughout the organism and then reach the skin (Fig. 4.11).

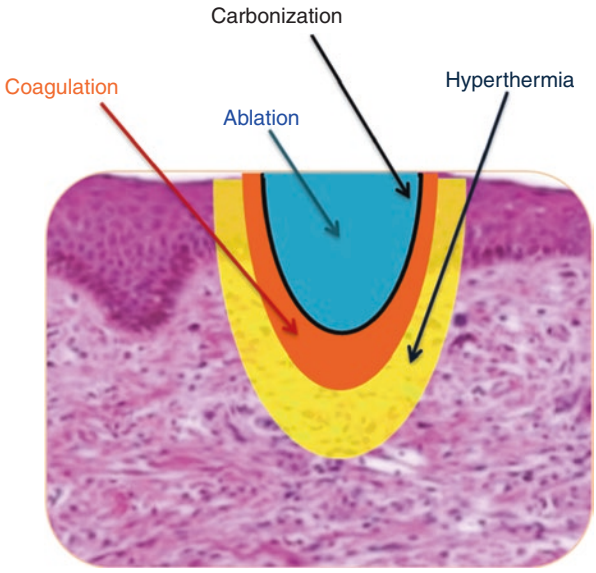

Fig. 4.9 Schematic drawing showing the action pattern on the skin of ablative fractional lasers. Ablation (vaporization) in the central area, a thin layer of carbonization, then adjacent coagulation, and, more externally, hyperthermia

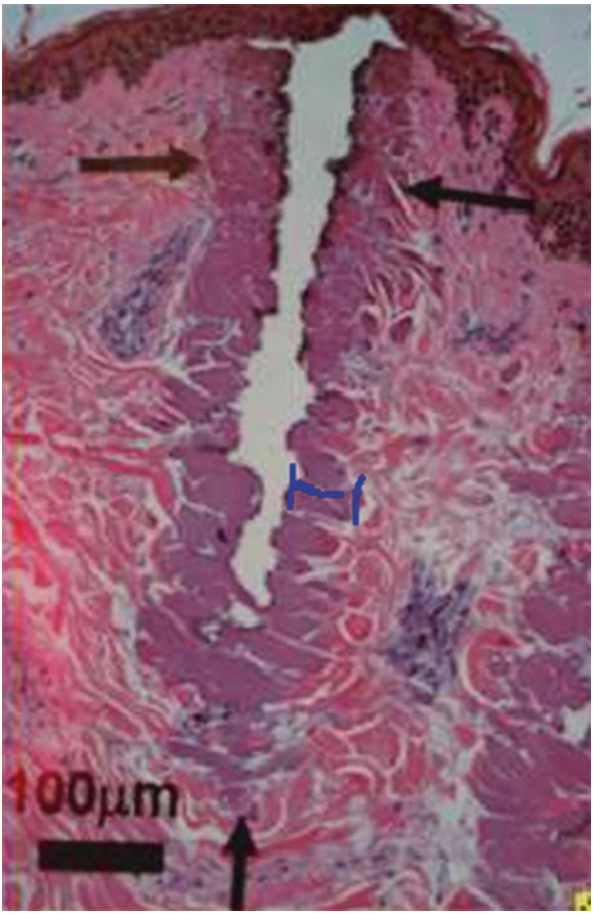

Fig. 4.10 Histological testing showing the action pattern on the skin of 10.600 nm wavelength (CO_2) laser. Note the extensive coagulation area adjacent to the central cleft generated by vaporization

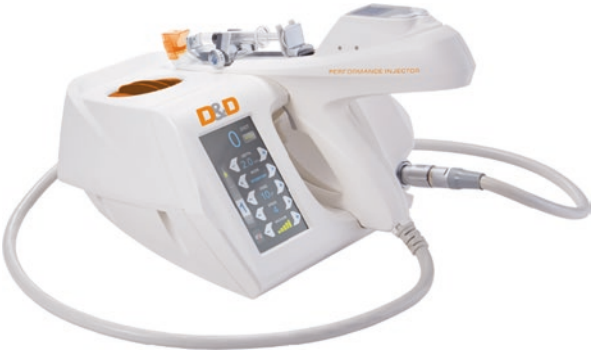

Fig. 4.11 Photograph of the D&D injector microneedle device

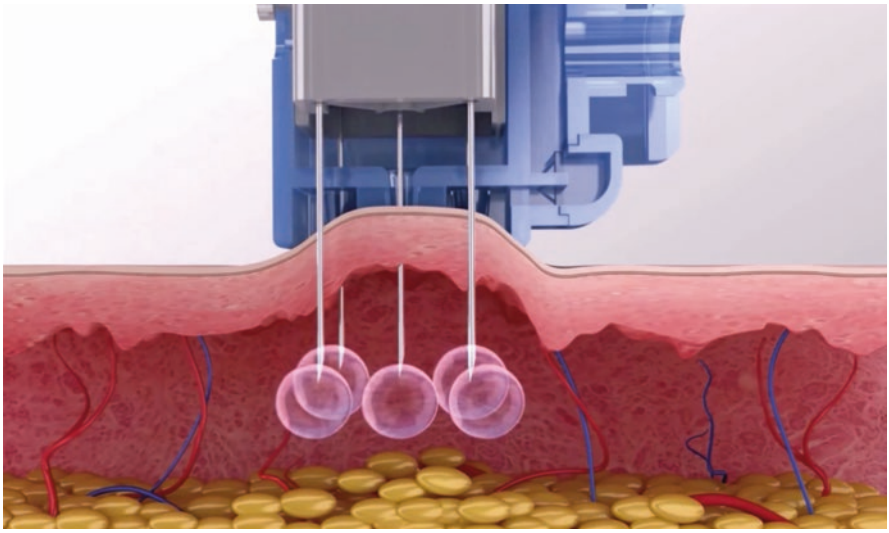

Fig. 4.12 Transdermal active delivery system using microneedles, with digital control

The device shortens the path of drugs to the skin and causes much lower concentrations to be used. It promotes transdermal infusion of water-soluble actives, macromolecules, and peptides. The negative pressure system (vacuum) reduces pain and improves coupling. The five and nine needle spots allow fast and homogeneous applications.

This device allows for a "delivery" of actives with virtually no downtime; with total control of infusion volume, infusing hydrophilic, lipophilic, and macromolecule drugs; and with total depth control, little sore afterward, is multipurpose and has low cost, and allows sterile substances (Fig. 4.12).

It is currently used for the following dermatological purposes: skin booster, rejuvenation, skin lightening (including melasma), hair treatment, infusion of botulinum toxin, flaccidity, filling, and disease treatment.

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Chapter 5
Microneedling and Drug Delivery

Célia Luiza Petersen Vitello Kalil and Clarissa Prieto Herman Reinehr

Introduction

Microneedling is a technique that optimizes the delivery of drugs, macromolecules, proteins, genetic materials, and vaccines through the stratum corneum; these molecules have a low permeation through the intact stratum corneum [1]. Drug delivery assisted by microneedling allows increasing the permeation of drugs with the use of a minimally invasive technique.

The use of microneedling to promote drug delivery is obtained through the permeation of the needles in the stratum corneum, allowing the delivery of the substances applied to the skin to the epidermis and avoiding contact with nervous fibers and blood vessels located in the dermis [1].

Mechanism of Action

Microneedling technique, also called percutaneous collagen induction, results in the liberation of cytokines immediately after the procedure, including interleukin-1a, interleukin-8, interleukin-6, TNF-a, and granulocyte and macrophage

All figures and tables were made by the authors of these chapters. Patients with pictures presented here gave written consent for the publication of their photographs.

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colony-stimulating factor, besides migration of keratinocytes, to repair epidermal damage caused by the micropunctures, and vasodilation [2]. Three healing phases are expected after trauma:

1. Initial injury/inflammation: platelets and neutrophils predominate; these cells release growth factors that will act in keratinocytes and fibroblasts (growth factors and TCF alpha and beta, platelet-derived and connective tissue growth factor).
2. Proliferative phase/healing phase: monocytes predominate; angiogenesis, epithelization, and fibroblast proliferation predominate, collagen III, elastin, proteoglycans, and glycosaminoglycans.
3. Remodeling phase/maturation: collagen III is slowly substituted by type I that will remain for 5–7 years. It is important to have in mind that this inflammatory cascade will only take place if the needles get to the dermis (needles should be at least 1 mm length).

How to Perform Drug Delivery

Drug delivery assisted by microneedling can be used for several indications, as presented in Table 5.1.

Microneedling produces several micropunctures that can be used as transportation routes of substances through biologic membranes, such as the stratum corneum [1]. For this purpose, needles should penetrate at least until the viable epidermis or to the superficial dermis.

The first microneedles available were made of silicon; later other materials were introduced, including alloy, stainless steel, ceramics, dextrin, maltose, and polymers [1]. Besides that, needles can be solid to create micropunctures and allow the permeation of substances applied immediately after the procedure, or hollows, in this case at the same moment the micropuncture is performed and the substance is injected. Microneedles can also be coated, covered by a thin external layer containing the substance of choice, or can be made with degradable polymers or

Table 5.1 Main indications for drug delivery assisted by microneedling

Melasma and spots
Rejuvenation
Striae alba and rubra
Dark circles under the eyes
Acne scars and traumatic scars
Treatment of dermatologic diseases
Androgenetic alopecia

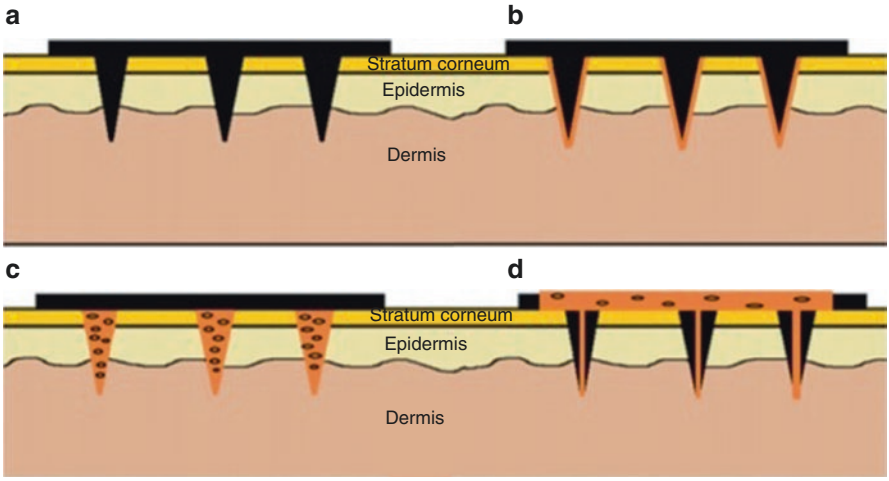

Fig. 5.1 Representation of solid needles (**a**), coated needles (**b**), biodegradable needles (**c**), and hollow needles (**d**)

Table 5.2 Different methods to perform drug delivery

Type of needles	Mechanism of action
Solid needles	Create micropunctures that allow permeation of substances applied to the skin immediately after the procedure
Hollow needles	Allow the delivery of substances contained in their interior during the microneedling procedure
Coated needles	Needles are covered externally with substances that are released at the time of needle penetration in the skin
Biodegradable needles	Applied to the skin, which slowly deliver the substance during the time they remain in place

carbohydrates, allowing the delivery of the substance at the time of the micropuncture, such as microneedles containing polylactic acid (Fig. 5.1 and Table 5.2) [1].

Biodegradable hydrogel needles have a different mechanism of action; after they are inserted in the skin, they promote the release of intercellular fluids that interact with the substance applied to the skin surface forming a continuous flux between viable epidermis, hydrogel microneedles, and the substance reservoir. Using this method the concentrations of the substance on the target tissue are higher than the one that occur with intradermal or intramuscular injections (Fig. 5.2) [3].

Although initially concerns regarding microbiological contamination of hydrogel microneedles have emerged, in a study with bacterial inoculation on the skin surface demonstrated that the microorganisms did not penetrate, possibly due to bacterial size that is much bigger than the drugs permeated through hydrogel, an hydrophilic material [4].

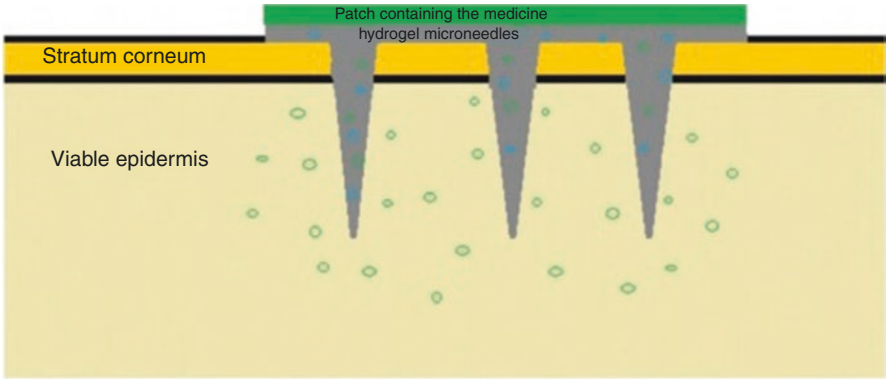

Fig. 5.2 Biodegradable hydrogel microneedles penetrate intact epidermis, intercellular fluid (blue circles) penetrates the microneedles, and a flux between the patch on the surface of the skin containing the drug is created; the result is the delivery of the drug to the epidermis (green circles). The flux of the drug persists until hydrogel microneedles and absorbed

The microneedles used for the procedure should always be of good quality, in a way they could assure an adequate strength of penetration without breaks during the procedure [1].

To effectively perform drug delivery with microneedling, it is important to reduce the stratum corneum barrier function, the main limiting for permeation of substances applied to the skin. Therefore, the correct knowledge about skin characteristics and variations should always be considered, with variations regarding sex, age, race, body mass index, and the area to be treated [1]. Based on this necessity, Laurent et al. evaluated skin thickness in 137 men and 205 women, including Caucasian, Asian, and Afro-descendants, and found that the mean skin thickness (epidermis and dermis) is 2.02 mm on the deltoid region, 2.54 mm on the suprascapular region, 1.91 mm on the waist, and 1.55 mm on the thighs; based on this study, we could observe that 1.5 mm length needles allow us to reach the dermis in all body areas [5].

Data regarding the ideal microneedle length for drug delivery are variable in literature; Bal et al. and Wu et al. demonstrated an increase of stratum corneum permeability with 150 μm to 400 μm microneedle length [2]. Later, Yan et al. analyzed several lengths (100 to 1100 μm) and densities (400 to 11.900 microneedles/cm^2) of microneedles to promote acyclovir delivery; the study demonstrated that needles lengthier than 600 μm were more effective to create microchannels and to increase the delivery of drugs. Moreover, lengthier microneedles with low densities (2.000 microneedles/cm^2) were the best ones to increase the drug flux [6].

The knowledge about the strength necessary to disrupt the stratum corneum, which has a thickness between 10 and 20 μm, and the viable epidermis, with thickness of 50 to 100 μm, is crucial [7]. The strength necessary to disrupt the "bricks and mortar" stratum corneum structure, represented by intercellular lipids and keratinocytes, is higher on the skin surface, because keratinocytes have lower water content;

this strength is reduced to the depth of the skin because keratinocyte hydration is gradually elevated. In summary, keratinocyte hydration results in "softer" keratin, which means less resistance to rupture [7]. When strength is applied to the skin for microneedle penetration, due to elastic characteristics of the skin some deformation occurs, and the total skin thickness is reduced by compaction; furthermore, indentation of epidermis toward the dermis occurs where the microchannels are located and not all needle length penetrates; sometimes only 30% of the microneedle length penetrates; that's the reason why many studies suggested using a least 1 mm length needles [8]. Based on these characteristics of the stratum corneum, some authors demonstrated that the use of automated systems, with controlled speed of microperforations, can produce more uniform micropunctures and increase the delivery of the drug desired.

Some characteristics of the device used to perform drug delivery should be observed: to increase permeation of drugs through the stratum corneum depends on some microneedle attributes; their length, power of cut, and the space among the needles (density) are the most important [2]. The strength necessary to penetrate increases directly proportionally to the areas of the needle tips; on this way, thinner microneedles penetrate easier.

The time microchannels created by microneedling remain open varies; information about how the closure occurs demonstrate that for needles with 370 and 770 μm in length, the channels remain permeable for an average time of 4–5 hours, and the complete closure occurs in 15–18 hours, and for needles with 1 mm in length the average time is of 8 hours [9]. Some procedures can retard the time of closure, such as occlusion, and microchannels can remain viable for up to 72 hours. Information about how this closure occurs, if it is uniform in all microchannels still needs more studies.

Medicines Used in Dermatology Already Studied

Drug delivery assisted by microneedling can be performed with substances of different molecular weights, varying from 538 Da to 72 kDa, as described by Verbaan et al. [10]. Next we will discuss some drugs used in dermatology that have evidence to support in microneedling-assisted drug delivery.

5-Aminolevulinic Acid and Methyl Aminolevulinate

In 2013, Torezan et al. compared the effect of traditional photodynamic therapy with the one associated with microneedling 1.5 mm length, performed immediately after the application of methyl aminolevulinate, and demonstrated safety and superiority with the method associated to microneedling [11]. Later, Chen et al. evaluated the effect of microneedling 4.0 mm length versus fractional ablative CO_2 laser

(AcuPulse 40AES-F, Lumenis Ltd.,Yokneam Industrial Park, 17.5 mJ/cm^2, densidade 5%) performed before 5-aminolevulinic acid application to the skin; microneedling promoted higher lateral diffusion of the drug than the laser on superficial dermis ($p < 0,05$), although no differences were observed in deeper dermis. Taking into consideration the cost of microneedling that is cheaper than fractional ablative CO_2 laser, we can obtain the same results with both procedures [12].

Tranexamic Acid

Comparing the injection of tranexamic acid versus topical application (4 mg/mL) immediately after 1.5 mm length microneedles in patients with melasma, treated in three monthly sessions, there was superiority of the technique associated with microneedling followed by drug delivery; improvement of melasma higher than 50% was observed in 41.38% of patients versus 26.09% in patients treated with microinjections [13].

Hyaluronic Acid

There is a study evaluating the use of hyaluronic acid patch containing 76 absorbable 650 μm length microneedles which were used in a pilot study to optimize the permeation of calcipotriol associated with betamethasone in psoriasis patients. Study protocol consisted on the daily application of calcipotriol plus betamethasone at night followed by the application of the patch containing hyaluronic acid microneedles during a week. Ten patients were treated; after a week the average improvement in PASI (Psoriasis Area Severity Index) was of 60%, without adverse effects reported. Besides promoting occlusion and hydration with the application of the hyaluronic acid patch, the patch allowed the delivery of calcipotriol and betamethasone [14].

Vitamin C

The use of vitamin C was described in a study for periorbital rejuvenation; a patch containing 153 absorbable microneedles with hyaluronic acid and vitamin C measuring 220 μm in length was applied twice daily and left for 6 hours before removal, during 12 weeks. The study compared the efficacy of treatment with other groups that used microneedles containing retinyl retinoate. Both groups showed treatments were effective and safe to reduce expression lines, demonstrating the potential of the technique to effectively deliver rejuvenating agents [15]. Other uses of vitamin C already studied include scar treatment and melasma treatment.

Bleomycin

Konicke et al. in a series of three cases associating 2.0 mm length microneedles for bleomycin 1 U/mL delivery during and immediately after the procedure for viral warts (total volume 0.2 to 0.5 mL for wart) demonstrated complete clearance of lesions after a mean of four sessions, with intervals of 15–30 days between sessions [16].

Ingenol Mebutate

Microneedling use with 0.5 mm length microneedles to increase ingenol mebutate permeation was described in a case report for treatment of field cancerization; four treatment areas were delimitated in the same patient: (1) only ingenol mebutate was applied, (2) only microneedling, (3) microneedling followed by the application of ingenol mebutate, and (4) application of ingenol mebutate followed by microneedling. The area treated with microneedling followed by the application of the drug achieved higher inflammatory reaction, erythema, and vesicle formation; besides that, only the two areas where combined treated were performed achieved improvement of lesions, while areas of isolated treatment did not show improvement [17].

Platelet-Rich Plasma

Studies evaluating platelet-rich plasma (PRP) have been performed for rejuvenation, treatment of scars, and alopecia. PRP associated with microneedling has been observed to be superior PRP alone; however studies are at initial phases and more evidence is necessary to indicate PRP use.

Adverse Reactions

Special attention should be given to products used in drug delivery; three case reports of foreign body granulomas after microneedling were reported when a commercial formulation containing vitamin C was used [18]. Commercial products are not appropriate for drug delivery because they contain preservatives, dyes, and other particles with immunogenic potential that could sensitize the patient.

Combination of Techniques

Microneedling Associated with Sonophoresis and Drug Delivery

The association of sonophoresis, an ultrasound that causes transitory cavitation of intercellular stratum corneum lipids with thermal and mechanic effects, with microneedling performed immediately after can potentiate glycerol delivery, elevating drug delivery up to 2.3 times higher with this combination when compared to microneedling alone [19].

Microneedling and Q-Switched Laser Associated with Drug Delivery

In a split-face study with 16 patients with recalcitrant melasma, patients were submitted to four monthly sessions: one side of the face was treated with Q-switched laser Nd:YAG 1.064 nm alone, and the other side of the face received treatment with laser followed by microneedling 1.5 mm in length (Dermapen®, Dermapen Company, Utah, USA) and application of vitamin C 0.025–0.05 mL/cm^2 (Redoxan-C ampoules 100 U/mL) for drug delivery. The study demonstrated superiority of the combination treatment, with ten patients showing good to excellent response versus two in the group that used only laser. Mechanisms of action proposed by the authors to justify the improvement observed with combination therapy include increase in dermal vascularization immediately after Q-switched laser that potentiates the delivery of vitamin C and its lightening effect and the improvement induced by microneedling in skin quality, which results in an increase in dermal thickness through neocollagenesis and production of elastic fibers [20].

Clinical Examples (Figs. 5.3 and 5.4)

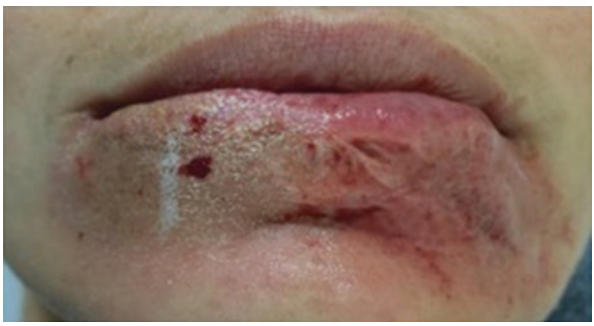

Fig. 5.3 Difference of immediate post-procedure end-point after microneedling (right side of the face) and CO2 fractional ablative laser (left side of the face): petechiae, erythema, and slight edema are observed in the area treated with microneedling

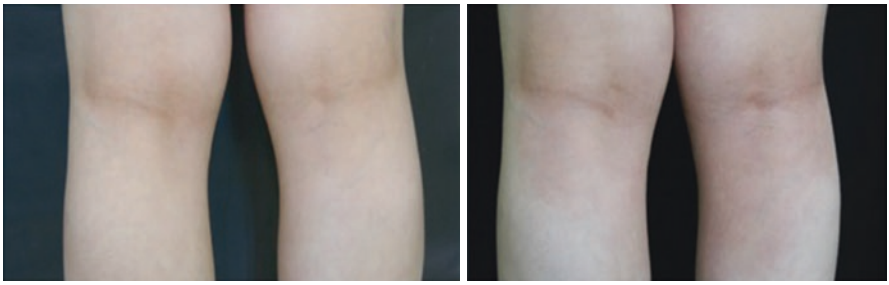

Fig. 5.4 Treatment of striae with 2.0 mm length microneedling before (picture on the left) and after three monthly sessions (picture on the right) followed by drug delivery of a serum anhydrous formulation containing hydroxyprolisilane 4%, omega active 5%, regestril 2%, matrixyl 3000 2%, and IGF 1.5%

Conclusion

Microneedling to promote drug delivery has a wide range of possibilities and indications. Scientific evidence is variable for each of the indications and substances studied, but we have observed an exponential increase in the number of studies performed in the past years, which tends to allow the realization of the technique with safety and efficacy, assuring quality to dermatologic procedures.

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Chapter 6
Intense Pulsed Light and Drug Delivery

Célia Luiza Petersen Vitello Kalil, Juliana Favaro, and Laura de Mattos Milman

Introduction

Intense pulsed light is a device that emits high-intensity, polychromatic, noncoherent, and uncollimated light, whose beams have wavelengths ranging from 400 to 1200 nm and pulse duration of 2 to 200 ms [9].

The IPL equipment consists of a chamber containing xenon gas, which is crossed by an electric current that releases pulses of energy in the form of luminous energy via a sapphire or quartz tip. The wavelength range is selected through the use of filters; only wavelengths above those blocked by the used filter pass through and reach the cutaneous surface [9].

The mechanism of action of the IPL is based on the capture of energy by tissue targets, called chromophores, whose principle is the selective photothermolysis. The three main chromophores are hemoglobin, melanin, and water, each with specific light absorption peak [9].

A versatility of the IPL allows the combination of parameters, aiming at treating the several vascular and melanocytic skin lesions, as well as performing epilation and photorejuvenation treatments, with a high skin coverage rate due its spot large size. It is a useful alternative when patients are unwilling to tolerate adverse effects of other procedures that require a longer recovery time. Thus, a IPL has an excellent cost-benefit ratio.

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The stratum corneum is an outer layer of the epidermis. It is composed of nonviable corneocytes, surrounded by an extracellular lipid matrix. Due their characteristics, only small molecular weight lipophilic permeants can passively diffuse through it [1].

A technique called drug delivery consists of finding methods to help cutaneous penetration of medicines, and this objective can be achieved through chemical, mechanical, and physical methods; IPL, mainly through its photothermal effect, is one of these methods [10].

IPL and Drug Delivery

The use of IPL and lasers has been widely studied as an approach to improve the permeation of drugs to facilitate their delivery through the skin. The breaking of the barrier function of the stratum corneum, through the use of lasers, can occur through direct ablation of the skin barrier, photomechanical waves, and photothermal effect, also present in IPL. The laser is useful for improving the permeation of a wide variety of permeants, such as small molecule drugs, macromolecules, and nanoparticles [1, 12].

Although the energy used to increase the absorption of drugs is much less than for the treatment of injuries or rejuvenation, the safety of using lasers and IPL must be taken into account. It is desired to optimize its use aiming at the balance between increased permeation and damage to the skin [1].

In IPL, transepidermal drug delivery occurs mainly due to the photothermal effect, when there is an increase in the permeability of the stratum corneum with a decrease in the skin barrier function, leading to increased penetration of the drugs for a short period of time, without affecting the skin viability.

The permeability of the stratum corneum by the thermal effect is transient, and the barrier function is restored after a few minutes. It is proposed that the application of the formula for drug delivery be carried out no later than 15 to 30 minutes after treatment with IPL [8].

In the case of the 1064-nm-long pulse laser, which is a non-ablative laser, there is a predominantly photothermal effect, just as in IPL. Studies have shown that after its application, there is an increase in the skin temperature (+13 ° C), which becomes higher as the irradiation continues and is higher in the irradiated center. The keratin becomes loose, the corneocytes fragile and scaly, leaving the cornea layer less concentrated and fragile, changing the barrier function of the stratum corneum; these effects are due to the photothermal effect [11].

Both macromolecules and nanoparticles are widely found from the stratum corneum to the dermis in the region exposed to the photothermal effect. Drugs of a lipophilic nature have their permeation favored, since the permeation mechanism is intercellular [8]. The presence of cosolvents delays the recovery of the barrier function, increasing the time for application after IPL; an increase in the depth reached by drugs is also observed.

In a study involving IPL, different sources of irradiation were applied to rat skin in vivo to increase the permeability of substances in the skin and improve the effectiveness of optical cleaning, which is based on the immersion of tissues in optical cleaning agents with the objective of reducing the dispersion and increasing the penetration of light into the tissue, which is limited by the epidermis barrier function, justifying the poor efficiency of optical cleaning of the skin by topical action. Regarding IPL, the pulse duration used was six milliseconds, shorter than usual, being, in the case studied, related not only to photothermal mechanisms but also to photoacoustic increase in skin permeability [12].

In the photoacoustic effect, characteristic of Q-switched lasers, there is a breakdown of the corneal layer, with the formation of small channels due to a great pressure that occurs through the application of high energy with a very short pulse duration (20 ns), which occurs with a minimal temperature rise [11].

IPL Indications

Vascular Lesions

It aims to reach the hemoglobin of the vessel. The filter is chosen according to the caliber and depth of the vessel.

Uses: Rosacea, telangiectasias, poikiloderma of Civatte, stretch marks, scars, angiokeratomas, hemangioma, port-wine stain, ochre dermatitis.

Possible drug delivery: Vitamin C, metronidazole, retinoic acid.

Melanocytic Lesions

In the treatment of melanocytic lesions, the objective is to reach melanin, which in most lesions is found in melanosomes of melanocytes and keratinocytes.

Uses: Solar melanosis, ephelides, café au lait spots, Nevus of Ota, infraorbital hyperpigmentation, postinflammatory hyperpigmentation.

Possible drug delivery: Tranexamic acid, alpha arbutin, hydroquinone, retinoic acid, vitamin C.

Epilation

The objective is, through thermal destruction, to reach the melanin present in the hair root, located in the deep dermis. The most used wavelength is 640 nm.

Active Acne

It acts both in the inflammatory process, through the 640 nm filter, and reduces the viability of *Cutibacterium (Propionibacterium) acnes* and that of seborrhea, through the 400 nm filter.

Possible drug delivery: Retinoic acid, salicylic acid, adapalene, azelaic acid.

Photorejuvenation

Minimally invasive technologies, such as IPL, have become increasingly popular in rejuvenation, being considered an approach among non-ablative ones. This trend resulted from the good safety profile, the short recovery time, and the versatility of these modalities. These factors are valued by doctors and patients, indicating a potential growth in non-ablative procedures [3, 7].

The wide range of IPL wavelengths allows its use to act on the different elements of skin aging:

- Longer wavelengths cause thermal damage to the dermis, inducing the activation of fibroblasts, with the formation of neocollagen.
- Shorter wavelengths are absorbed by melanin and oxyhemoglobin present in pigmentation disorders and telangiectasias.

Therefore, all visible elements of aging (fine wrinkles, sagging, telangiectasias, irregular pigmentation) are improved with a small rate of adverse effects and rapid recovery.

Possible drug delivery: Hyaluronic acid, retinoic acid, vitamin C.

Photodynamic Photorejuvenation

IPL can be used in combination with 5-aminolevulinic acid (5-ALA) in the treatment of photoaging, pre-neoplastic lesions, such as actinic keratoses and acne.

Photodynamic therapy requires a photosensitizer, with ALA being the most used in dermatology, as a topically applied agent that acts as a prodrug, which is preferentially absorbed by cells that divide rapidly in the epidermis and superficial dermis; with light activation, it is transformed into a highly photoactive porphyrin derivative, producing free radicals that cause selective cell destruction [5, 6].

Originally developed to be used with red or blue light, to treat premalignant lesions and superficial skin neoplasms, 5-ALA has been used more recently in combination with several light sources, including IPL, increasing the effectiveness of non-ablative therapies [2]. Regarding the choice of the filter, the desired photothermal effect must be considered.

Due to the lack of penetration depth and the interference of melanin, the effects of photodynamic therapy with blue light are, for the most part, purely photochemical. The combination of the photothermal effects of IPL with the photochemical effects of photodynamic therapy has demonstrated an improvement in the cosmetic result. The longer wavelengths emitted by IPL not only have enough energy to activate the photochemical process, but they also have wavelengths long enough to effectively reach multiple chromophores. Photodynamic therapy with IPL is very effective in exciting porphyrins, achieving a synergy between the photochemical effects of reactive oxygen species and the heat-induced effects of selective photothermolysis. In addition, the shorter incubation time of 5-ALA allows for better patient tolerance during treatment and, subsequently, less adverse effects in the postoperative period [13].

IPL and Studies Related to Drug Delivery

Studies exploring the use of IPL for drug delivery are far less numerous than those related to lasers.

The use of topical polyphenols associated with IPL has been studied by Freedman [3, 4]. It has increased interest in exploring the effects of topical antioxidants of botanical origin, such as green tea extract and rosemary, which contains polyphenolic compounds with antioxidant properties, with the ability to prevent lipid peroxidation induced by ultraviolet radiation, DNA damage, and carcinogenesis. Clinically, topically applied polyphenolic antioxidants have been shown to decrease inflammation, prevent erythema and photoaging, and may have a protective effect on facial skin exposed to high-intensity visible light radiation [3].

In a study Freedman et al. assessed whether the topical application of polyphenolic antioxidants to skin treated with IPL would reduce the adverse effects derived from exposure to light, such as erythema and increased lipid peroxidation. Ten volunteers underwent three IPL sessions on the face, 3 weeks apart. A polyphenolic antioxidant solution was applied pneumatically to the left side of the face, starting immediately before the first IPL treatment and weekly completing six treatments. The concomitant use of polyphenolic antioxidants reduced lipid peroxidation and dehydration of the skin treated with IPL. Polyphenolic antioxidants could then provide a protective effect on facial skin and increase the effects of IPL therapy [4].

The same author studied the association of IPL and topical polyphenolic antioxidants in rejuvenation in 30 patients, the result being assessed through skin biopsy, cutaneous levels of polyphenolic antioxidants, levels of skin hydration, and clinical evaluation. Patients were randomly placed in three groups: three IPL sessions at 3-week intervals; use of an antioxidant solution with topical polyphenols with pneumatic application for 6 weeks; and three sessions of IPL associated with six applications of topical antioxidant, and when performed in the same session, the antioxidant application was performed immediately before the IPL treatment [3]. The group in which IPL was associated with antioxidants, in relation to IPL alone, presented

greater thickness of the epidermis and papillary dermis, decreased lipid peroxide concentration, increased skin moisture content, and increased levels of polyphenolic antioxidants ($p < 0.05$). There was also a qualitative improvement in hydration, texture, and pore size, in addition to a reduction in erythema and blisters. In relation to the group that used antioxidants alone, the association with IPL demonstrated a greater thickness of the papillary dermis, qualitative improvement in the reduction of fine lines, and reduction of hyperpigmentation. The study suggests that the combination of these therapies would create synergy and optimize results in non-ablative facial rejuvenation [3].

Interest in the study of the association of 5-ALA with IPL has also grown, and it is expected to increase the benefit of IPL in the treatment of photoaging.

Marmur and collaborators, in a pilot study, evaluated the ultrastructural changes observed in the treatment for photorejuvenation with the association of ALA and IPL. Seven patients (six women, one man) with minimum photodamage had their face treated with two sessions of IPL, with an interval of 1 month, and half of the face was applied topical ALA 1 hour before the procedure. Biopsies were performed before and 3 months after the end of treatment in order to detect changes in collagen by ultrastructural analysis using electron microscopy. An increase in type I collagen fibers was observed after treatment in all patients, and this increase was greater on the side that received associated ALA, suggesting that the result of the association would be higher than IPL as the only treatment in photorejuvenation. The expected result would be even greater in patients with greater photodamage, since the stratum corneum less preserved in these patients would facilitate the penetration of ALA. Side effects were minimal, lasted less than 24 hours, and were seen on both sides of the face [6].

A prospective, randomized, controlled study with 20 patients also studied this association. Each patient received a total of five IPL sessions across the face, spaced for 3 weeks. Before the first three sessions, topical 5-ALA was applied to half of the face 30 to 60 minutes before treatment with IPL. The use of 5-ALA resulted in an improvement in global photodamage (80% versus 45%), mottled pigmentation (95% versus 60%), and fine lines (60% versus 25%) in addition to greater patient satisfaction. Both were well tolerated, with no significant increase in adverse effects with the use of 5-ALA. The reported adverse effects included erythema, purpura, and edema, most of which resolved in 1 to 2 days, with maximum duration of 5 days [2].

Another study evaluated this association in 16 patients with mild to moderate photodamage and with at least 3 facial actinic keratoses, in which half of the face was treated with short contact with ALA (30–60 minutes) followed by IPL and the other half with IPL only. There were three sessions with a monthly interval. Thirteen patients completed the study. Three months after the end of treatment, an improvement was found in the group that received 5-ALA in all signs of photodamage: “crow’s feet,” skin roughness, mottled pigmentation, and telangiectasias, in addition

to a decrease in actinic keratoses. The authors suggest three sessions of IPL associated with photodynamic therapy with ALA instead of the traditional five or six sessions of IPL as single therapy. The most common adverse effects, erythema and edema, were observed in less than 10% of cases and occurred on both sides of the face [5].

Illustrated Uses of the Use of IPL in Practice

See Figs. 6.1 and 6.2 for understanding this subject and better information about this.

Rosacea

See Fig. 6.1.

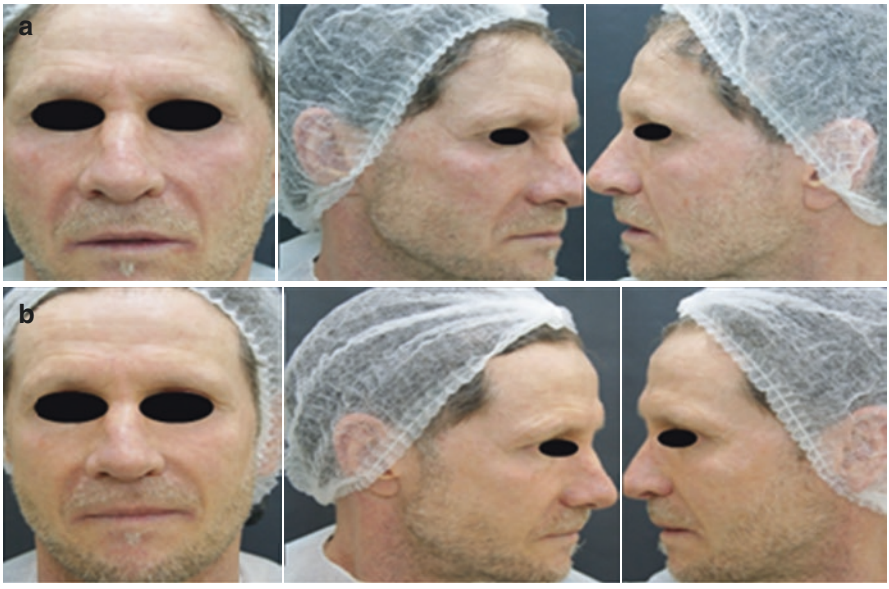

Fig. 6.1 (**a**) Before treatment. (**b**) Twenty days after three IPL sessions with drug delivery. The formula used for drug delivery was compound by: telangyn®, rosage®, calmaline®, etoxidiglicol, MDIComplex®

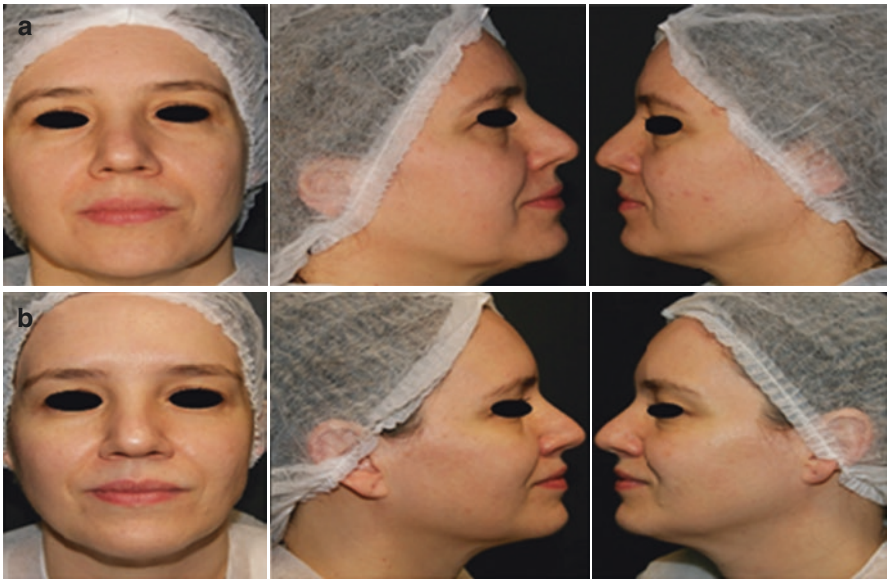

Fig. 6.2 (**a**) Before treatment. (**b**) Twenty days after four IPL sessions with drug delivery. The formula used for drug delivery was compound by: acneaol®, nicotinamida, calmaline®

Acne

See Fig. 6.2.

Cautions

Some precautions must be taken before choosing the IPL; reported below:

- Attention must be paid to the phototype, especially if above IV; IPL should not be used on phototype VI or on tanned skin, and adequate sun protection must be provided for at least 30 days after the procedure;
- Caution should also be exercised in patients with melasma, and consideration should also be given to previous evaluation using Wood's light to detect possible subclinical melasma;
- Extrafacial areas must have the parameters adjusted, as they have a reduced number of pilosebaceous follicles in relation to the face, and healing takes longer for this reason.

Complications with IPL can be avoided by taking the correct care; they occur mainly due to repeated and overlapping pulses, use of excessive energy, or inadequate selection of patients. When a certain temperature threshold is reached,

epidermolysis may occur, perceived as graying of irradiated skin or protein denaturation with the formation of dermal fibrosis. In addition to erythema and edema, vesicles may form; crusts with consequent dyschromias usually temporary; and scars (rare).

Conclusion

IPL treatment facilitates the penetration of active ingredients into the skin by drug delivery, mainly due to the photothermal effect. Studies on this subject are extremely limited, but the evidence presented suggests that we can always take advantage of the post-procedure moment to apply specific assets in order to optimize results.

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Chapter 7
Fractional Non-ablative Laser and Drug Delivery

Juliana Favaro and Vivian Barzi Loureiro

Introduction

Fractional lasers work according to the theory of selective photothermolysis, and the tissue target (chromophore) is water. The light energy is absorbed by the target and is transformed into heat, causing selective thermal damage and creating microscopic vertical channels of vaporization (ablative laser) or coagulation (non-ablative laser), while surrounding healthy tissue remains intact and unaffected [1].

Non-ablative lasers emit light within the infrared range (1000–1600 nm) of the electromagnetic spectrum. The most used wavelengths are 1340 nm, 1410 nm, 1440 nm, 1540 nm, and 1550 nm. The major clinical indications are rejuvenation and treatment of scars and stretch marks, by the neocollagenesis process [2–4].

Like ablative systems, non-ablative devices aim to resurface skin through thermal induction of collagen remodeling in the dermis, by targeting water as its primary chromophore.

Ablative lasers remove the epidermis, while non-ablative lasers work by heating up the underlying skin tissue, without harming the surface [5].

The wavelengths are weakly absorbed by the superficial layers of skin, thereby penetrating the deeper tissues, creating a dermal wound without disruption of the epidermis and the stratum corneum, keeping its integrity. Therefore, non-ablative lasers have shorter recovery times (downtime) and fewer side effects, like persistent erythema, infection, hyperpigmentation, or scars [2, 3].

The selective and controlled warming of the dermis causes protein denaturation, which induces the collagen remodeling [3, 6].

The laser-assisted drug delivery may be an interesting way to optimize the desired results (Fig. 7.1).

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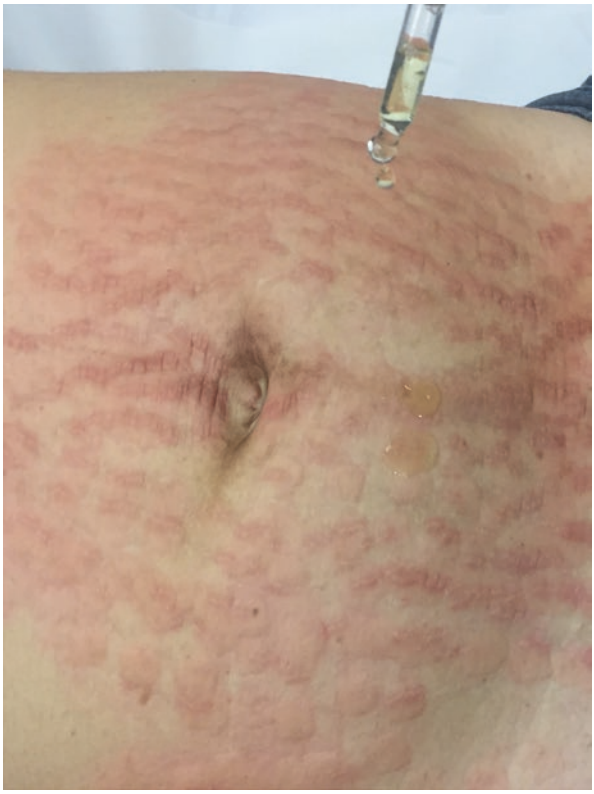

Fig. 7.1 Drug delivery post NAFL

Drug Delivery

The primary function of the skin is to act as a barrier, protecting the organism from external injuries. It is selective and semipermeable, limiting the cutaneous absorption of exogenous substances.

The stratum corneum is the outer layer of the skin (epidermis), made up of corneocytes (anucleated keratinocytes that have reached the final stage of keratinocyte differentiation) and extracellular lipid matrix. This network is organized in a "bricks and mortar" formation. The stratum corneum is a dense and cohesive layer, and it serves as the primary and effective barrier between the body and the environment.

In normal conditions, only small molecular weight (<500 Da) lipophilic permeants can passively diffuse across intact skin [7, 8].

Topical application of drugs is an advantageous way of administration because it spares the first hepatic metabolism that occurs with the oral administration/when the medication is taken orally. Nevertheless, it is easier and more comfortable than injectable application.

However, the transcutaneous absorption is limited by the compact structure of the stratum corneum [9].

The tissue-laser interaction may enhance the skin permeation, increasing the assimilation of substances applied topically on the surface of our body – drug delivery. Thus, it is possible to improve the therapeutic goal.

The benefits of drug delivery go beyond dermatology aesthetics. It allows us to treat skin disorders as vitiligo, actinic keratosis, non-melanoma skin cancers, cancerization field, viral warts, and hemangiomas [10].

The use of ablative lasers (CO_2 10,600 nm, Erbium:YAG 2940 nm) for drug delivery is well-known, and its efficiency has been studied and confirmed in many clinical trials. Different, small, and macro molecules are being used such as ALA (168 Da), methyl ALA (182 Da), imiquimod (240 Da), diclofenac (296 Da), ingenol mebutate (431 Da), methotrexate (455 Da), prednisolone (358 Da), triamcinolone (434,5 Da), amorolfine (354 Da), tranexamic acid (157 Da), tretinoin (300 Da), ascorbic acid (176 Da), lidocaine (234 Da), 5-FU (130 Da), botulinum toxin (150 KDa), and polylactic-L acid (140 KDa) [11].

However, limited data are available regarding the application of the non-ablative fractional laser technique for drug delivery, compared to ablative fractional lasers.

Recent evidence suggests that non-ablative fractional photothermolysis may also improve uptake of topical drugs [12].

A preliminary study has shown increased transcutaneous delivery of ALA with non-ablative fractional laser pretreatment, with minimal side effects.

Photodynamic therapy (PDT) consists of a chemical reaction between a photosensitizer and a specific wavelength of light energy, generating reactive oxygen species and free radicals to induce cell death. Effective transdermal delivery of photosensitizer is an essential step for PDT.

Photosensitizers, as ALA, produces protoporphyrin. By measuring porphyrin fluorescence, it is possible to observe the transcutaneous penetration of the drug.

A case series of patients with acne vulgaris demonstrates that non-ablative fractional laser, applied immediately prior to PDT, may enhance ALA skin penetration. Laser treatment was performed with a 1550 nm fractional erbium glass laser, and settings were 20 and 50 mJ (energy), density of 50/cm^2, using a 10×10 mm spot size handpiece. ALA incubation time was set to 30, 60, or 180 min. Porphyrin fluorescence imaging was performed. Non-ablative fractional laser-pretreated areas showed significantly increased porphyrin fluorescence compared to non-pretreated areas. Laser energy strength and ALA incubation time were positively correlated with ALA absorption. The fluorescence intensity tended to increase with increasing laser energy. However, the difference between 20 and 50 mJ was statistically significant only after incubation for 180 min [12].

Non-ablative lasers deliveries focused and controlled thermal damage while keeping the surface intact. Histopathological assessments of skin reveals no sign of epidermis destruction. There is no true ablation. However histologically undetectable transient loosening of this layer may occur. It means that the laser induces a functional disruption of dermal-epidermal junction.

It is believed that the laser induces transient formation of a permeable lacunar system within the stratum corneum, justifying the enhancement of skin permeability/permeation [12, 13].

Increased transepidermal water loss was reported after non-ablative fractional laser, contributing to the theory of the temporary functional disturbance of the stratum corneum, induced by the laser. The loss rate and the tissue healing were proportional to the density set [14].

The measurement of electrical impedance after non-ablative laser treatment dropped significantly, indicating reduction in skin barrier resistance [15].

Animal models and preliminary initial studies have supported the use of Erbium:glass 1550 nm (Sella evo) improves transepidermal absorption of topical agents and also macromolecules (>40 KDa) and nanoparticles. Laser settings: 30 mJ, density 256 or 529 spots/cm2 [10].

Histological analysis showed dermal-epidermal cleavage after laser treatment, endorsing junction disturbance, without destruction of the epidermis above [10].

Drug delivery's uses go beyond the regular dermatological indications. Gant and Banga demonstrated the increased transdermal permeation of diclofenac sodium and sumatriptan for migraine treatment, using non-ablative home devices [16].

The laser drug delivery increased absorption cause concern about potential systemic side effects and toxicity associated with the drug. Another drawback is the possibility of bacterial infection by not using sterile substances.

According to literature, the risk of *S. aureus* and *P. aeruginosa* infection linked to non-ablative laser treatment is not different than the rate with skin intact. Thus, the non-ablative devices present lower risk of secondary infection than the ablative laser, because the surface is preserved [16].

Advantages of non-ablative lasers, comparing to ablative ones, are increased patient tolerability, reduced post-procedural downtime, and side effects (erythema, swelling, changes in color, infection, and scarring). The risks are higher in colored and tanned skin, extra facial areas, and use of aggressive parameters. The drug absorption seems to be more related to density than energy.

The possibilities of drug delivery are vast, and many substances might have their penetration increased by the use of laser. So, the potential therapeutic benefits are also huge [17].

Previous literature has demonstrated the use of ablative lasers to enhance drug permeation. However, studies about drug delivery and non-ablative laser are more recent and scarse. Even so, the results, so far, are very positive and encouraging. Further studies using a large group of humans or patients are needed to confirm and clarify the findings.

Expertise Tips

Taking into account all the discussions above, we suggest applying topical actives immediately after the non-ablative laser treatment. So, we are able to improve the desirable outcome (Table 7.1).

Table 7.1 Possible use of drug delivery in association with NAFL and suggested active drugs

Dermatologic indication	Possible drug
Photoaging	Vitamin C Retinoic acid Hyaluronic acid Hydroquinone Tranexamic acid
Stretch marks Atrophic scars	Vitamin C Retinoic acid Hyaluronic acid
Hypertrophic scars Queloides	Triamcinolone
Areata alopecia	Triamcinolone
Androgenic alopecia	Finasteride Minoxidil Growth factors Biotin
Actinic keratosis Field cancerization Non-melanoma skin cancer	Pre-PDT photosensitizers (ALA, MAL) Imiquimod 5-Fluororacil

Clinical Indications

- Rejuvenation.
- Atrophic scars.
- Stretch marks.
- Hypertrophic scars/keloids.
- Vitiligo.
- Androgenetic alopecia.
- Alopecia areata.
- Non dermatological indications: analgesia, vaccines (Fig. 7.2).

Contraindications (for Laser)

- Active inflammation or infection on the site of treatment.
- Pregnancy.

Contraindications (for Drug)

- Allergy/hypersensibility.

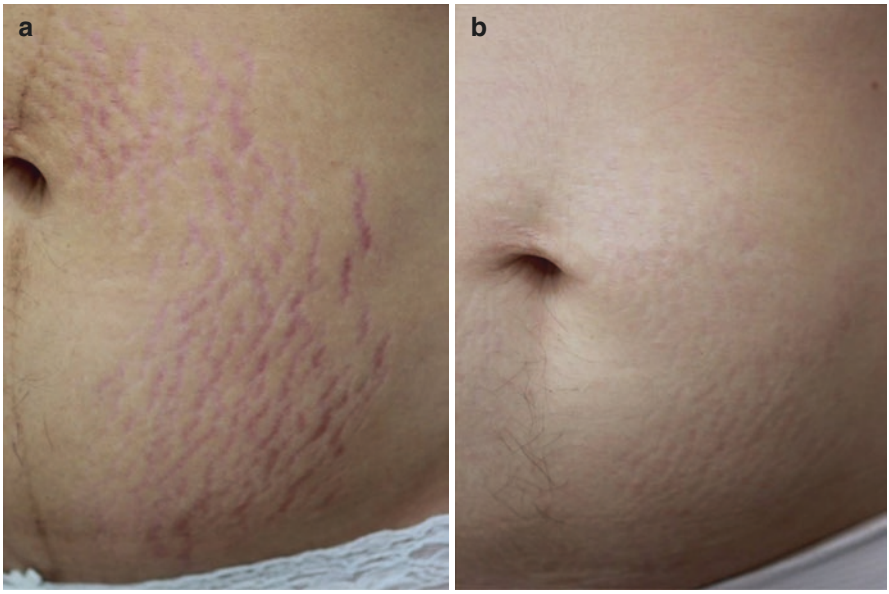

Fig. 7.2 (**a**) Stretch marks: pretreatment. (**b**) Stretch marks: posttreatment (four sessions NAFL + drug delivery)

Precautions

- Cleaning.
- Cooling the surface.
- Application of the drug immediately after the laser.

Posttreatment Orientation

- Cleaning with water an soap, twice a day.
- Herpes simplex prophylaxis.
- Analgesia, if necessary.
- Topical retinoic acid, if hyperpigmentation.
- Topical emollient/healing cream.
- Topical retinoic acid, if hyperpigmentation.

Possible Complications (Laser)

- Eryrthema.
- Edema.

- Bruising/Purpura.
- Hyperpigmentation.
- Scars.
- Infection.
- Herpes simplex.

Possible Complications (Drug)

- Hypersensibility.
- Contact dermatitis.
- Toxicity (specially with anesthetic).
- Systemic side effects related to the drug.
- Infection.

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Chapter 8
Ablative Fractional Lasers and Drug Delivery

Valéria Campos, Mariana Silveira Ferreira Mylius, and Fernanda Musa Aguiar

Introduction

Ablative fractional lasers aim to partially remove the epidermis in a controlled manner. They were launched as a consequence of the need for a more conservative treatment for moderate and severe photoaging, but with shorter post-procedure and less adverse effect than traditional ablative lasers (Fig. 8.1). Two technologies are representatives of this type of lasers, namely, *erbium:yttrium-aluminum-garnet* (Er:YAG,

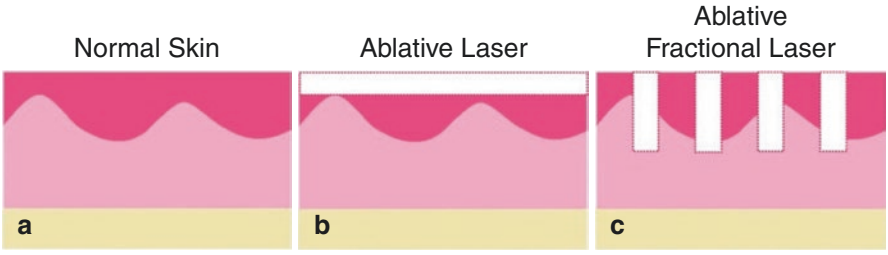

Fig. 8.1 Schematic representation of the skin according to laser use: normal skin (**a**), ablative laser (**b**), and ablative fractional laser (**c**)

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2940 nm) and fractional carbon dioxide (CO_2, 10,600 nm) lasers; both have water as target chromophore.

The application of fractional photothermolysis microscopically produces zones of thermal damage that can reach even the reticular dermis, interspersed with untreated areas. This effect is called thermal micro-zones (TMZs). The benefit of the technique includes the areas remaining intact, which promote rapid recovery of epidermis. There is dermal remodeling with neocollagenesis and tissue contraction.

The technique of laser-assisted drug delivery was first described in 1987. Since then, several lasers have been used for this purpose. The purpose of this method is to make it easier for the medication to reach its target, with the advantage of requiring less of the medication and reduced adverse events.

The *stratum corneum* has the main function of defense and, therefore, produces a barrier for penetration of exogenous substances, mainly for hydrophilic molecules and those greater than 500 Da, reducing the absorption of topical medication by 1–5%, which makes topical application less effective. Different strategies, including chemical, mechanical, or physical, are used to temporarily increase skin permeability without causing prolonged damage to the barrier. Several studies have observed that, when using these techniques, it was possible to perform the passage of cutaneous and transcutaneous macromolecules of up to 20,000 Da, such as erythropoietin and human growth hormone.

By creating a real access through the formation of vertical micro-tunnels through epidermal ablation with penetration to the dermis, that is, treated areas interspersed by untreated areas, ablative fractional lasers have been one of the first choices for drug delivery.

Types of Ablative Fractional Lasers

The main representatives of the group are *erbium:yttrium-aluminum-garnet* and fractional CO_2 lasers.

The fractional CO_2 laser has a wavelength of 10,600 nm and has tissue water as a chromophore. It acts in a controlled manner in the vaporization of the epidermis, without excessive thermal damage to adjacent tissue, which reduces the risk of scarring and permanent depigmentation. Its penetration into the skin depends on its water content, with no interference on the presence of melanin or hemoglobin in the treated area. Table 8.1 indicates additional features of fractional CO_2 lasers.

The mechanism of action of fractional CO_2 occurs through heating and consequent vaporization of tissue water at the moment the laser reaches the skin, generating skin ablation. During the process, there is also transfer of heat to adjacent tissues, promoting denaturation of collagen and consequent tissue retraction and future neocollagenesis.

Er:YAG 2940 nm laser, because of its greater affinity for water, requires less energy to perform tissue ablation. Its innovative feature is the generation of

Table 8.1 Characteristics of fractional CO_2 and Er:YAG lasers

	Fractional CO_2 laser	Er:YAG laser
Wavelength	10,600 nm	2940 nm
Target	Tissue water	Tissue water
Water absorption coefficient	800/cm	12,000
Average pulse duration	<1 ms	0.25 ms
Tissue penetration (estimated by J/cm^2)	20–30 μm	1–3 μm
Minimum fluency required for skin ablation	5 J/cm^2 [a]	0.5- 1.5 J/cm^2 [a]

Er:YAG (*erbium:Yttrium-aluminum-garnet*) [a] This value can vary depending on laser power and skin moisture at the time of application

long-lasting pulse that promotes dermal coagulation around the ablation micro-zones, deepening and widening the TMZ coagulation column. There is involvement of dermal vessels in clotting, which reduces bleeding during the procedure compared to older equipment using shorter pulses and that caused bleeding.

Thermal Micro-Zones

Thermal micro-zones (TMZs) are produced by ablative fractional lasers. They consist of vertical ablative micro-channels surrounded by coagulated tissue that penetrate the *stratum corneum* (Fig. 8.1), allowing direct access to the epidermis and/or dermis. There are two parameters that are variable and may be adjusted when performing drug delivery using ablative fractional lasers: density and depth of TMZs. By adjusting these parameters, it is possible to adjust the amount of drug used, influence its biodistribution, decrease the time between application and drug contact with its target, and, consequently, obtain a more efficient and early clinical response.

The density of TMZs determines the area of treated skin, which varies according to the number of open channels in a given skin area and the size of the spot. Decreasing the distance between TMZs, the percentage of treated skin increases. Initially, it was believed that the greater the density, that is, the more TMZs were created, the more access channels and the greater the absorption of the drug. The findings suggest that there is a minimum density necessary to achieve maximum permeation of the drug, but there will be no progressive increase in permeation with increasing density. This is perhaps due to the excess of tissue damage or drug depletion, which generates a decrease in the concentration gradient. In vitro studies have shown an increasing cumulative increase in the drug on the skin with increasing density to up to 5% coverage; above this parameter, no additional benefit was observed, and there was even a decrease in permeation with the use of very high densities.

TMZ depth represents the innermost level reached by the micro-channel in the skin; it is mainly controlled by the pulse energy used for a given laser. Channel depth directly influences drug delivery. However, studies have been shown to be

ambiguous regarding the deposition of drug in the tissue according to channel depth. It is suggested that there is a dependence of drug deposition on the depth for hydrophilic to slightly lipophilic medications (e.g., methotrexate, prednisone, and diclofenac) and an independence of deposition in relation to lipophilic drugs, including lidocaine, ingenol, and imiquimod.

TMZs remain open 30 minutes after ablative fractional laser. The fraction drops to 89% after 60 minutes, 75% after 6 hours, and only 3% after 24 hours of the procedure.

Drug Delivery

The efficacy of any drug therapy depends on its ability to penetrate different tissues and thus reach its target. In the skin, the *stratum corneum* is the main limitation for absorption of medication, especially if it has a very high molecular weight or is hydrophilic. By breaking the skin barrier and allowing contact with the lower portion of the epidermis and dermis, an alternative path is opened for drug entry in the body.

For a better understanding of medication diffusion in the tissue, one must first understand Fick's laws. In 1855, Adolf Eugen Fick, a German doctor, described the equations of mass transport by diffusion. They explain the movement of molecules in the tissue also observed in the cutaneous penetration of medications.

Diffusion is the random movement of particles from a high concentration region to a low concentration region. It is postulated that the transfer rate of diffused substance per unit area of a section is proportional to the concentration gradient measured perpendicularly to that section. From this hypothesis, Fick's law is obtained, which can be described by the formula in Fig. 8.2.

Fig. 8.2 Fick's formula

$$J = \frac{A.D.Kp\,(c_1 - c_2)}{h}$$

A = Contact Area

D = Diffusion Coefficient

Kp = Participation Coefficient

$C_1 - C_2$ = Concentration Difference

h = Distance between Drug and Target

From the equation, it can be inferred that flow (J) is directly proportional to contact area (A), concentration difference (c_1–c_2), diffusion coefficient (D), and participation coefficient (Kp), being inversely proportional to the distance between drug and target (h), that is, the greater the distance, the lower the flow.

When TMZs are created, there is a change in flow. For the same drug, diffusion and participation coefficients are fixed, as well as concentration differences between external and internal environment; when making a channel into the epidermis and dermis, we reduce the distance between drug and target and increase contact area, thus facilitating flow. In Fig. 8.3 we can better understand what was exposed.

TMZs allow the drug to reach deeper portions of the skin, which increases its diffusion into the tissue. Theoretically, when the target is deep, the deeper the TMZ, the shorter the distance between drug and its target, increasing drug entry flow (remember that distance and flow are inversely proportional); and the greater the opening of TMZ, the greater the area of contact between drug and skin, which will increase flow, since these are directly proportional parameters. However, in some cases in dermatology, the target is superficial, such as the epidermis, and the use of deeper TMZs is not justified.

We emphasize that these theoretical applications are not always seen in practice even when the objective is to reach vessels below the epidermis. In the drug delivery study of lidocaine and ethylglycinexylidide using Er:YAG, for example, serum concentrations of medications were observed according to the depth of TMZs. There was no detection of medication in the blood after its topical application, without the use of intervention, that is, without opening TMZs. Serum peak of both lidocaine and ethylglycinexylidide was observed at a depth of 250 μm and not at a depth of 500 μm, as initially expected. The results were also comparatively smaller for the depths of 25 and 50 μm. Serum measurements were taken 90 and 120 minutes after application, and in both measurements, the depth of 250 μm was found to be greater.

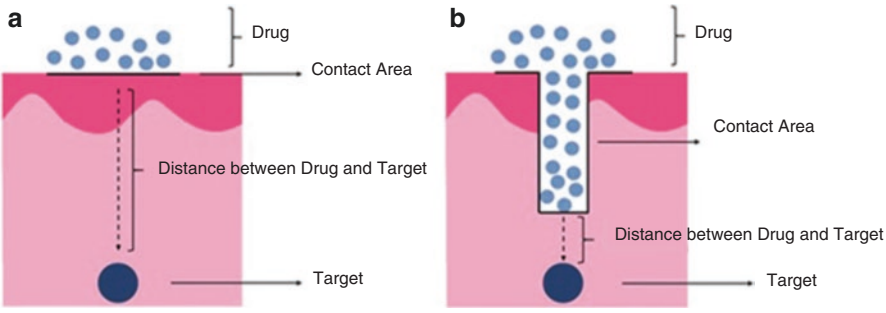

Fig. 8.3 Schematic representation of Fick's law: On the left (**a**), drug disposition in the application of topical medication without any type of intervention. On the right (**b**), drug distribution after performing ablative fractional laser with TMZ opening, with increased contact area and reduced distance between drug and target

The authors believe that this occurred because dermal vessels are located in porcine skin in greater quantity in the most superficial portion of the dermis, which allowed better absorption of medication. In addition, it is postulated that there is greater denaturation of viable tissue when deepening TMZs, which consequently also decreases drug absorption.

It is believed that by filling TMZs with the drug-containing formulation, reservoirs of medication are created and act by maintaining a higher concentration gradient of the drug in the external environment, which allows a sustained diffusion for a longer period of time.

The difference in concentration and participation coefficient depends on the vehicle used. The diffusion coefficient depends on the weight of the molecule used. The greater its weight, the greater the resistance created for its movement, which will result in a lower diffusion coefficient. Therefore, molecules of high molecular weight are less absorbed.

Vehicle Choice

When using fractional lasers for drug delivery, one should choose drugs with hydrophilic vehicles. The fluidity of the substance and the presence of co-solvents in the formulation also increase drug penetration. The proliferation of microorganisms can be hindered by the use of anhydrous formulations. The indiscriminate use of products intended for full skin is very reckless; however there is still no consensus in the literature on the need to use sterile substances, especially when working with more superficial TMZs. In addition, it is important to remember that we often work in a non-sterile environment and there is contamination from the skin microbiota, even after proper asepsis.

Indication of Ablative Fractional Laser-Assisted Drug Delivery

Drug Delivery of Aminolevulinic Acid (ALA) and Methyl-Aminolevulinic Acid (MAL)

There are several clinical and preclinical studies of drug delivery of 5-aminolevulinic acid (ALA) and methyl-aminolevulinic acid (MAL) after ablative fractional lasers. These substances are precursors of porphyrins and are used topically for photodynamic therapy (PDT) in the treatment of several dermatological diseases, such as actinic keratoses, Bowen's disease, actinic cheilitis, superficial basal cell carcinomas, and onychomycosis.

In 2014, Haedersdal et al. carried out a preclinical study on pig skin, which compared the penetration and biodistribution of MAL and ALA after treatment with ablative fractional CO_2 laser. The results showed that laser pretreatment alters the kinetics and biodistribution of these substances, favoring penetration into deeper skin structures.

In 2015, Cai et al. compared the use of isolated CO_2 laser with that associated with PDT-ALA for the treatment of Bowen's disease. Eighteen patients were selected with 22 tumor lesions confirmed by histopathological examination and were randomized into 2 groups. One group was treated with CO_2 laser associated with topical ALA and PDT and the other group only with CO_2 laser. The lesions in the first group showed 72.73% complete remission and 9% recurrence; however, the second group showed greater recurrence of lesions, 45.45%. This difference was statistically significant.

In the study by Ko et al., it was demonstrated that the association of PDT-MAL with Er:YAG 2940 nm laser was significantly more effective and showed less recurrence in the treatment of all grades of facial actinic keratoses compared to PDT-MAL alone, including in the thickest lesions. Recurrence rates were lower in the first group and adverse effects were higher, but well tolerated.

The treatment of actinic cheilitis with PDT does not provide results as satisfactory as that of actinic keratoses. Choi et al. selected 33 patients with actinic cheilitis, confirmed by histological examination, to be randomized to receive a session of Er:YAG 2940 nm laser associated with PDT-MAL or 2 sessions of PDT-MAL. The first group showed a significantly more effective response at the 3- and 12-month follow-up, in addition to less recurrence at 12 months.

Figures 8.4 show a patient with multiple actinic keratoses treated with a single CO_2 laser session and drug delivery with MAL, before and 30 days after.

Drug Delivery of Methotrexate

Methotrexate is a medication widely used in the treatment of psoriasis and rheumatoid arthritis and can be administered orally, intramuscularly, intravenously, intrathecally, and subcutaneously. This drug has little percutaneous bioavailability because it is hydrophilic and because of its high molecular weight. In an in vitro study performed on rat skin to assess transcutaneous delivery of methotrexate, Lee et al. observed an increase of 3–80 times, according to the flow used, of permeation with the use of Er:YAG 2940 nm laser. Another preclinical study in pig skin in vitro showed that the same ablative laser significantly increased the delivery of topical methotrexate. The deeper areas of TMZs had higher concentration of the substance than the more superficial layers, which indicates that the depth of TMZs may be important for the delivery of hydrophilic molecules.

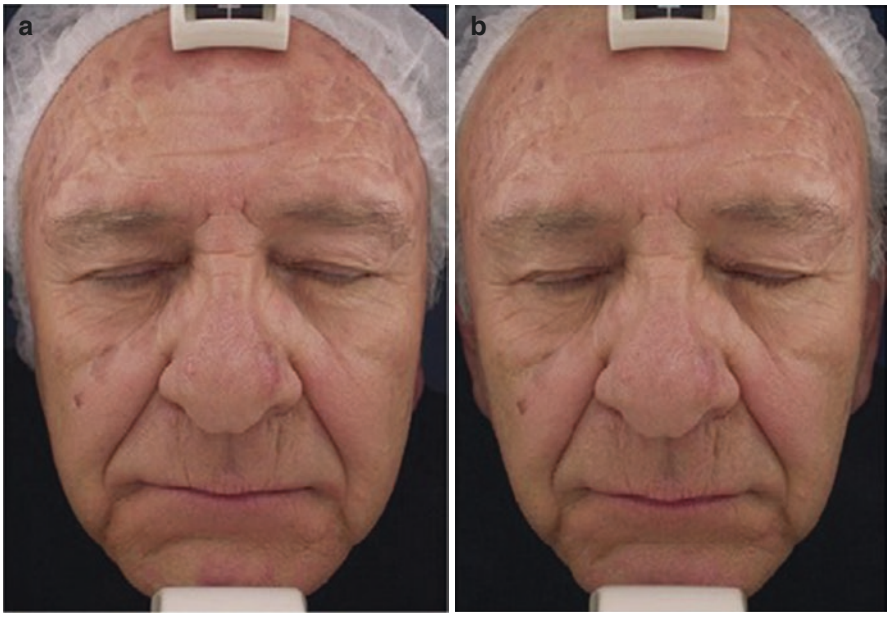

Fig. 8.4 Patient with multiple actinic keratoses, before (**a**) and after 30 days (**b**) of treatment with CO_2 laser (tip, 800; 14 mJ/50 mzt) and drug delivery with MAL

Drug Delivery of 5-Fluorouracil

Topical 5-fluorouracil is widely used in the treatment of actinic keratoses, superficial basal cell carcinoma, and squamous cell carcinoma in situ; however its skin penetration is limited. In the study by Wenande et al., it was demonstrated that the previous application of CO_2 laser increases and accelerates the absorption of 5-fluorouracil, with more uniform deposition of the substance in deeper layers of the skin.

Nguyen et al. evaluated the efficacy and safety of treating superficial basal cell carcinoma and squamous cell carcinoma in situ with CO_2 laser associated with drug delivery of 5% 5-fluorouracil under occlusion for 7 days. After 8 weeks of treatment, a biopsy of the scar was performed, which confirmed histological healing in 87% of lesions. Mild local adverse effects such as erythema and erosion have been reported.

Drug Delivery of Ingenol Mebutate

Braun et al. reported a case of cancer field treatment with Er:YAG associated with drug delivery of 0.015% ingenol mebutate on one side of the occipital region and the substance alone on the other. There was a more intense inflammatory reaction on the side that was pretreated with ablative fractional laser.

Drug Delivery of Lidocaine

A study carried out in pigs showed that pretreatment with ablative fractional laser at low energy and drug delivery of topical lidocaine significantly increases the absorption of this substance. Bachhav et al. studied the effect of TMZ density, produced by lasers, on permeation of lidocaine. The authors concluded that a minimum density of TMZs is necessary for maximum drug penetration, but the increase in these channels does not provide greater delivery. Yun et al., in a randomized, split-face clinical trial, evaluated the efficacy of 5% lidocaine cream applied after Er:YAG laser for facial resurfacing. Anesthesia on the side where the laser was applied was more effective and faster than the side of conventional topical anesthesia.

Drug Delivery of Topical Antifungals

Treatment of onychomycosis with topical antifungals is generally ineffective, as these drugs have difficulties in penetrating the nail blade. Many patients have contraindications to the use of systemic therapy due to adverse effects, comorbidities, and drug interactions. Studies on ablative fractional laser-assisted drug delivery have shown good results. These lasers produce ablative columns that remove nail tissue containing fungi and facilitate medication penetration. Bhatta et al. obtained good results with the use of terbinafine cream assisted by CO_2 laser. The most studied substances were terbinafine, luliconazole, and amorolfine creams.

Drug Delivery of Botulinum Toxin

Mahmoud et al. evaluated the effect of topical botulinum toxin type A, applied immediately after CO_2 laser in the treatment of periorbital wrinkles. On one side of the eyes, saline was applied as control. The side tested with botulinum toxin showed significant improvement in wrinkles 30 days after application.

Drug Delivery of Timolol

Ma et al. evaluated the efficacy of drug delivery of timolol assisted by CO_2 laser in nine patients from 1 to 6 months of age with profound infantile hemangioma. Laser sessions were performed at week intervals, with the following parameters: fluency 25–30 mJ/pulse, 5% density, and single pulse. Topical eye solution of 0.5% timolol was applied under occlusion for 30 minutes, 4–5 times a day, for an average of 14.2 weeks. Patients showed clinical improvement, assessed by the hemangioma activity score, from moderate to excellent. No patient had any complications or side effects.

Drug Delivery of Corticosteroids

The use of corticosteroids in association with fractional lasers was suggested by Waibel et al. for hypertrophic scars. Fifteen patients were treated using fractional CO_2 and immediately applying triamcinolone acetonide suspension. Three to four applications were performed 2 to 3 months apart. Final evaluation was made 6 months after the last application with improvement of hypertrophy, texture and dyschromia.

Park, Chun, and Lee's study evaluated ten patients with keloids in the left shoulder from BCG vaccination. Treatment consisted of applying Er:YAG laser to the entire lesion, which was subsequently divided into two parts. In one half of the lesion, intralesional corticosteroids were subsequently applied by injection. In the other half, occlusive corticosteroids were performed for 3 hours. Four sessions were carried out with a 6-week interval. After 42 days of the last session, patients were evaluated. A greater reduction of lesions was observed in the group treated with intralesional corticosteroids compared to the group treated with topical medication ($p < 0.05$).

The study of the technique in alopecia areata was carried out with two patients using fractional CO_2 and subsequent application of triamcinolone acetonide with the aid of an ultrasound. There was complete recovery after just a single session.

Li et al. applied the CO_2 and drug delivery technique to patients with vitiligo in the extremities. Twenty-five individuals were studied, with hemibodies divided into case and control. The intervention protocol consisted of performing fractional CO_2 in a hemibody, followed by application of betamethasone solution and UVB-NB phototherapy. In the control group, that is, in the other hemibody, only CO_2 was performed, followed by phototherapy. The results demonstrated a better repigmentation of the test side with respect to the control (40% versus 8%, $p < 0.05$).

The experiment by the author of the book, Valéria Campos, MD, was in a single plate of alopecia areata treated with Er:YAG 2940 nm laser followed by application of a triamcinolone-containing preparation, with excellent response.

Drug Delivery of Vitamin C

The use of vitamin C was studied by Waibel et al. in association with vitamin E and ferulic acid. The objective of the research was to evaluate whether the use of fractional CO_2 with application of serum containing 15% vitamin C, 1% vitamin E, and 0.5% ferulic acid would influence the healing of skin lesions. Although the result was not statistically significant, acceleration in the healing of the treated hemiface was observed, proven by increasing the concentration of fibroblast growth factor in the molecular analysis of biopsies.

A 2003 study by Lee found increased bioavailability of vitamin C in the dermal layer when applied after performing fractional CO_2, Er:YAG, or dermabrasion.

Figure 8.5 shows a patient treated with CO_2 laser and drug delivery of vitamin C, before and 1 month after the session. Figure 8.6 shows a patient before, 15 days and 30 days treatment with CO_2 laser and drug delivery of hyaluronic acid.

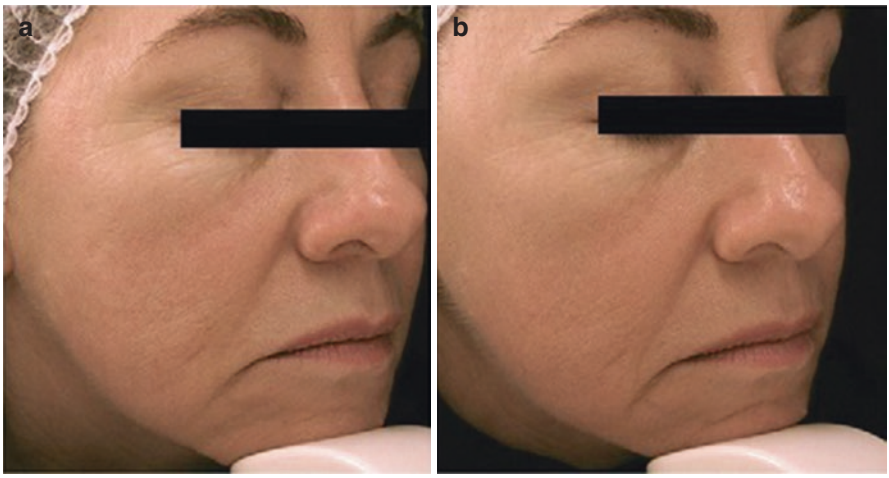

Fig. 8.5 Patient treated with CO_2 laser and drug delivery of vitamin C, before (**a**) and 1 month after (**b**) a single session

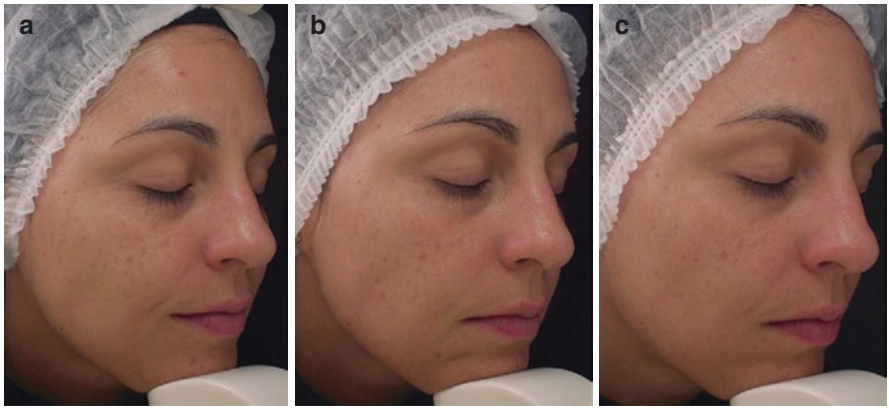

Fig. 8.6 Patient before (**a**), 15 days after (**b**), and 30 days (**c**) after treatment with CO_2 laser and drug delivery of hyaluronic acid

Drug Delivery of Polylactic Acid

Polylactic acid associated with fractional CO_2 was studied by Rkein et al. for treatment of atrophic scars. The photographs of baseline and 90-day lesion after the combined application of CO_2 and polylactic acid were evaluated by four blind observers who reported an overall improvement of lesions, as well as improvement in atrophy, dyschromia, and scar contour.

Drug Delivery of Platelet-Rich Plasma (PRP)

A study involving platelet-rich plasma and the use of fractional laser was published by a South Korean group. The purpose of the research was to assess whether there was an additional benefit of PRP for rejuvenation. Of the 22 treated patients, 11 underwent the therapeutic combination, and the other half underwent only laser application. All patients received treatment three times, being evaluated at the beginning and 1 month after the last session. A subjective improvement noted by the patient was observed, in addition to an objective improvement in skin elasticity with reduction in the grade of erythema.

Drug Delivery of Kligman's Formula

The use of Kligman's triple formula and the use of fractional CO_2 for melasma was studied by Trelles et al. Three groups of female patients of phototypes II to IV were evaluated. The first group used only topical treatment with triple formula; the second one performed fractional CO_2 alone, and the third group combined the use of fractional CO_2 with topical therapy. The subjective improvement assessment using the MASI (Melasma Area and Severity Index) scale was made at month 0, 1, 2, 6 and 12, and the satisfaction index was calculated. In the first month, all groups reached the maximum score in the satisfaction index; however, during evaluations, the satisfaction of groups with only topical or CO_2 treatment fell, maintaining the maximum graduation in the combined group. There was a statistically significant result of improvement in melasma ($p < 0.001$) both for MAIS scale and satisfaction index of the combined group in relation to individual therapies.

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Chapter 9
Q-Switched and Drug Delivery

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Introduction

The Q-switched laser (QS) is a non-ablative laser that has been growing in the dermatology field. It has been used for tattoo removal, epilation, for treatment of vascular and pigmentary lesions, and even for dermal remodeling seeking non-ablative resurfacing. Its use can be optimized through the drug delivery technique, which seeks to optimize the cutaneous penetration of medicines, through chemical, mechanical, and physical methods, with the QS laser being one of them.

Lasers emit a monochromatic light whose energy characteristics, pulse duration and exposure time, can be focused and manipulated according to the desired photobiological effect [1]. In this context, non-ablative Q-switched lasers emit ultrashort waves, in the order of nanoseconds, with high energy peaks, which completely disorganize keratin and corneocytes, forming micropores/microchannels in the stratum corneum with minimal elevation of temperature. This effect results from photomechanical waves, which transiently elevate the permeability of the stratum corneum, through the mechanical effect, without removing it [2, 3]. In tattoo removal, there is also an acoustic effect.

These changes allow an increase in skin permeation that can last for up to a week after the laser is performed, allowing the drug delivery procedure to be performed during this period [3, 4]. Furthermore, by creating true micropores/microchannels in the stratum corneum, both lipo- and hydrophilic molecules, as well as

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macromolecules, can benefit from this increased permeation [3]. Q-switched lasers increase the permeation of molecules by at least 12 times compared to intact skin. However, the use of active ingredients with ideal physical-chemical characteristics, the use of cosolvents in the formulation, and the selection of an appropriate, low-viscosity, polar vehicle can considerably increase the bioavailability of the applied drug and, consequently, the therapeutic response [5].

In addition, the procedure performed with Q-switched laser is practically painless and has no downtime, favoring the patient's adherence to the proposed treatment. Also, the effect of the laser alone as a promoter of rejuvenation and its lightening effect act in synergy with the application of the specific formulation for drug delivery, with superior results when compared to the use of the isolated techniques.

The Effect of Photochemical Waves

Photomechanical waves are secondary to the use of lasers with ultrashort waves, lasting nanoseconds. The photomechanical waves promote expansion of the lacunae spaces in the lipids of the stratum corneum, due to the high amplitude of transient pressure applied on the skin, creating pores/channels for permeation of molecules, and also cause changes in cell membranes, facilitating the transcellular pathway (Fig. 9.1) [2, 6]. This expansion of the extracellular space extends to the deep layers

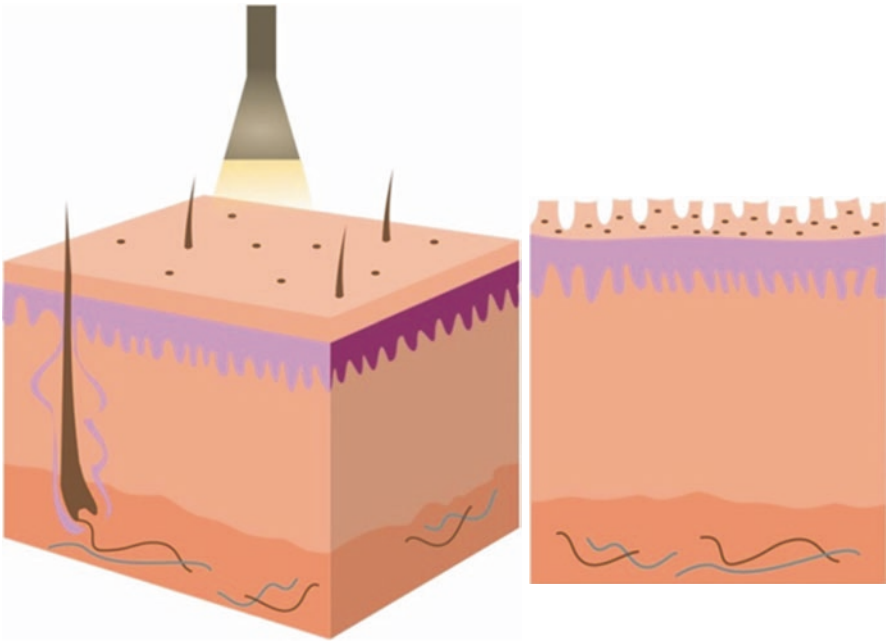

Fig. 9.1 Effects of photomechanical waves creating microchannels in stratum: (**a**) before laser and (**b**) creation of these microchannels by the laser

of the stratum corneum, while the granular stratum remains unchanged [6]. Depending on the wavelength and the energy utilized, it is also possible to observe a total removal of the stratum corneum and an increase in the permeation of the molecules, mainly the hydrophilic.

The transport of the applied active ingredients on the skin after laser application occurs by diffusion through the micropores/microchannels created [6].

There are modifications that increase the permeation of cell membranes, without affecting cell viability, that last a few minutes and allow the delivery of drugs and active ingredients to the intracellular environment (Fig. 9.2) [7, 8]. This delivery

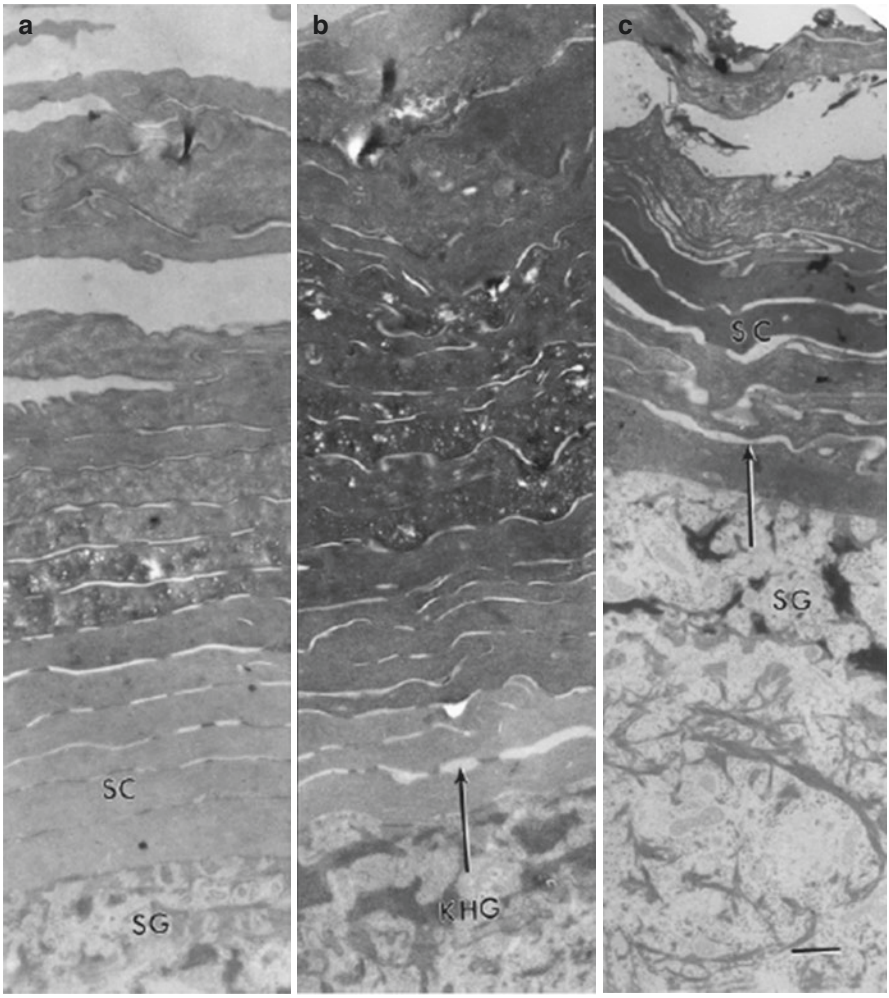

Fig. 9.2 Electron microscopy in low magnification of stratum corneum and granulosum after exposition to (**a**) a single photomechanical wave, (**b**) a single photomechanical wave and solution containing sodium lauryl sulfate, (**c**) ten photomechanical waves. Arrows indicate the expansion of extracellular space in inferior stratum corneum layers, observed in (**b**) and (**c**). KHG, keratohyalin granules. (Adapted from: Menon et al. [6])

occurs through the diffusion of molecules adjacent to the cell surface, by a pressure gradient. The presence of a cosolvent, associated with the procedure, facilitates the expansion of lamellar spaces, including intercellular ruptures in the granular layer, increasing the transport of molecules, mainly the hydrophilic ones [9]. The association of a cosolvent acts selectively on the lamellar lipids in order to favor drug delivery.

Q-Switched Lasers and Studies Related to Drug Delivery

Alteration of the Skin Barrier Function by Lasers

QS Menon and collaborators, in a study using electron microscopy after the application of a 694 nm ruby Q-switched laser, observed that only the stratum corneum was injured post the procedure, while the nucleated keratinocytes and dermis were not affected and remained viable [6]. The authors consider that the finding occurs due to the fact that the stratum corneum has a different structure from the other layers of the epidermis.

According to Liu et al., which evaluated real-time variations in the temperature of the skin surface immediately after performing a Q-switched Nd:YAG 1064 nm laser, the maximum elevation of the skin temperature 1 minute after the end of the procedure was 1.01 ± 0.23 °C [3]. This finding corroborates with the idea that the photothermal effect, which could assist in the promotion of drug delivery, does not exist with the application of Q-switched lasers, since there is no heating of the stratum corneum. The same study compared the permeation of glycerol, a hydrophilic agent with difficulty to penetrate into the intact stratum corneum, after application of a 1064-nm-long pulse Nd:YAG laser and after the Q-switched laser, and observed that both had a similar ability to increase permeation of the molecule up to 12 times on the day of the procedure. Through histopathological analysis, the authors demonstrated that 5 days after the procedure, microporous/microchannels in the stratum corneum were still present, although on a lesser scale; on the 14th day, the stratum corneum was intact [3].

The delivery of macromolecules into the lower layers of the dermis and epidermis, through drug delivery mediated by Q-switched laser, is also described. Lee and colleagues, in a 1998, reported the delivery of 40 kDa dextran (average diameter 8.8 nm) and 20 nm diameter latex particles enhanced by the use of a Q-switched ruby laser with a single shot per area, reaching a maximum penetration of 20 μm in the dermis; the same study demonstrated that this increase in the permeation of macromolecules is ephemeral, with a reduction in permeation after 2 minutes of the procedure [10]. In a subsequent study by the same author, in 2001, it was demonstrated the possibility of increasing the penetration of dextran 40 kDa by manipulating the characteristics of the photomechanical waves; when using photomechanical waves in a confined ablation system with Q-switched ruby laser, the permeation

depth was increased from 50 to 400 μm, allowing delivery to the dermis [11]. In 2002, the authors studied the permeation of suspended fluorescent microspheres of 100 nm in diameter, containing sodium lauryl sulfate, an agent that favors skin permeation, and observed that the particles were delivered to the lower layers of the epidermis after a single shot of Q-switched ruby laser, demonstrating the potential of this technique for drug delivery of larger molecules, such as DNA plasmids and encapsulated drugs. Sodium lauryl sulfate permeating agent causes enlargement of the lacunae spaces in the stratum corneum and delays the recovery of the epidermis barrier function; however it is a potentially irritating agent for the skin [12].

The use of Q-switched laser for even deeper drug delivery, reaching systemic circulation, has been studied with 6 kDa insulin. The study using a ruby laser was carried out in two stages: at first, sodium lauryl sulfate, a surfactant that delays the recovery of the cutaneous barrier of the stratum corneum, was applied to the skin and a laser shot was made; then, the insulin solution was applied to the skin and a second laser shot was made; as a result, there was a reduction in blood glucose during the 3 hours that followed the experiment, of approximately 80% compared to baseline, demonstrating a systemic effect of insulin applied on the skin [13].

Melasma

The QS laser has an increasing role in the treatment of pigment disorders due to its photomechanical effect on melanocytes and on melanogenesis. The laser leads to decreased transport of melanosomes through keratinocytes and also causes dendritic destruction of melanocytic branches. The drug delivery technique using bleaching agents aims to optimize the laser treatment. Vitamin C, a peroxidase inhibitor, decreases melanin synthesis and has been used in drug delivery with different technologies for melasma treatment. The combination of the 694 nm Q-switched ruby laser and sonophoresis, followed by the immediate application of vitamin C for drug delivery, was studied in 26 patients attaining lightening of the skin after 4 to 6 biweekly sessions, with a reduction of MASI (Melasma Area and Severity Index) from 15.51 ± 3.00 to 10.02 ± 4.39 3 months after the end of treatment. Most patients (73%) did not present post-inflammatory hyperpigmentation or presented only mild post-inflammatory hyperpigmentation, resolved in 1 week. Only one patient had severe post-inflammatory hyperpigmentation, which lasted for more than a month [14].

Another study with eight patients evaluated the use of 1064 nm Q-switched Nd:YAG laser across the whole face for the treatment of melasma in four monthly sessions, associated with the ultrasonic application of vitamin C in one hemiface as drug delivery. It was observed the superiority of the combined technique compared to the isolated use of the laser. In the 3-month follow-up, there was no record of rebound or post-inflammatory hyperpigmentation [15].

A third study evaluated the application of vitamin C after two different technologies for promoting drug delivery, the QS-Nd:YAG laser and microneedling,

with microneedling being performed immediately after laser treatment [16]. Sixteen patients with recalcitrant dermal or mixed melasma underwent four monthly sessions: one hemiface was treated with QS-Nd:YAG laser followed by microneedling (Dermapen®, 0.5 and 1.5 mm) with vitamin C drug delivery (Group A) and the other hemiface with the QS-Nd:YAG laser only (Group B). With monthly clinical evaluation and MASI score, the patients were monitored for 6 months after the end of treatment. The group which submitted to the association of treatments had a significantly lower mean MASI score and a better response to treatment than Group B, according to the clinical evaluation. According to MASI scores, in Group B, 2 patients had a good response, while 12 did not respond to treatment. A good or very good improvement was reported by 10 patients in Group A and by only 3 patients in Group B. The adverse effects and recurrence rates were similar in Groups A and B (31.3% and 43.8%, respectively); two patients dropped the study due to hyper- and hypopigmentation. Bearing in mind that the QS-Nd:YAG laser causes mechanical effects on melanocytes and on melanogenesis, by itself, it is already expected an beneficial effect on melasma, which can be optimized with the application of vitamin C, as previously mentioned. When associated with microneedling, a technique that promotes skin whitening and drug delivery, the authors suggest that the QS-Nd:YAG laser would increase blood circulation in the dermis, thus increasing the microneedling effect and the penetration of vitamin C and also suggesting that the association of these treatments has a synergistic effect. The authors suggest sessions with longer intervals (monthly instead of biweekly) to prevent post-inflammatory hyperpigmentation and highlight the similar recurrence of melasma in both groups, suggesting the use of topical bleaching agents for at least 6 months after the end of the treatment [16].

To assess the effectiveness of the Q-switched Nd:YAG laser in combination with 7% alpha arbutin solution (Skin Advanced Laboratory, Japan) in the treatment of refractory melasma, a prospective study with 35 patients performed ten weekly laser sessions, followed by two more sessions with monthly intervals and topical application of 7% alpha arbutin solution twice daily. Alpha arbutin has been shown to be a potent tyrosinase inhibitor, without the side effects of hydroquinone. An independent observer rated melasma severity on a 5-point scale at each visit. After the 6 months of treatment, 30% of the individuals had the results classified as excellent in the lightning of melasma (reduction of 81%), and 36.7% had a good response (reduction of 51–80%). Alpha arbutin could not only be considered a maintenance therapy, as it remains between laser applications, but also a drug delivery, in view of the beginning of use right after laser application, when there would still be an increase in permeability due to the photoacoustic effect of the laser. Mild and transient side effects included discomfort during treatment, erythema, bleaching of fine hair, and hives. Three cases of mild hypopigmentation and two cases of melasma recurrence were recorded [17].

The association of QS laser with glycolic acid peeling has also been studied. Surface peels have their role well established in melasma, acting in the removal of melanin from the epidermis. Glycolic acid is an alpha hydroxy acid with smaller molecular size and has better penetration into the epidermis and inhibitory effect on melanin synthesis, modulating tyrosinase activity [18, 19].

In one of the studies, 16 female patients with phototypes III and IV underwent 6 weekly sessions of Q-switched Nd:YAG 1064 nm laser and 3 biweekly sessions of 30% glycolic acid peeling. When performed in the same session, the peeling was performed immediately after the laser application, and the acid contact time was 1 to 2 minutes, according to the patient's tolerance. The most common side effects were erythema and transient burning, which disappeared in 3 hours. Superficial flaking was resolved with emollient use. After the six sessions, both sides had significant improvement, and it was greater in the combined treatment group (32.6% versus 22.0%). The authors consider that the removal of the epidermis provided by the peel could allow the reaching of deeper lesions in the dermis without serious side effects; being this technique useful in the treatment of mixed melasma, they also mention a shorter contact time, a lower acid concentration used, as well as the possibility of using lower laser energy as a benefit of the association [18].

A second study evaluated the same association in 15 male patients with melasma. Five sessions of Q-switched Nd:YAG 1064 nm laser were performed, with glycolic acid 30% peeling being applied in one hemiface before the laser, in the same session. The peeling was applied for 2 minutes, with an increase of 30 seconds in each session according to the patient's tolerance. Patients were followed up for 12 weeks, and 12 of them completed the study. The maximum bleaching reached, assessed through colorimetry, was seen in the fourth week and was of 52.3% with the combined treatment and of 37.6% with the laser only. Worsening was seen in the eighth week and at the end of the follow-up. The most common side effects were burning and pinching and occurred on both hemifaces. One patient presented desquamation on the side of the association, resolved with application of topical corticosteroids; two patients with phototype V had dyschromia on the entire face after the last treatment, and one of them remained with guttate hypopigmentation, unresolved during the follow-up period. The authors believe that the superior results of the combined treatment are due to the removal of epidermal pigmentation by the peeling and by the improvement of laser penetration. They conclude that, although the combination of treatments provides a temporary reduction in melasma in men, the incidence of side effects and the risk of worsening melasma with inflammation, which can be aggravated by combined treatment, does not justify its use [19].

Therefore, the association of laser and peeling seems to have a better result potential than when the techniques are used alone, but the best substance used for the peeling, the contact time, the concentration, and the adjustments of the laser parameters according to the association are not yet established, needing caution and further studies.

Rejuvenation

QS lasers have been used for photodamage and rejuvenation treatment, since no epidermal ablation is produced by this procedure. They allow effective treatment, with less risk of prolonged erythema and thermal damage after treatment [17]. The use of antioxidants, bleaching agents, as mentioned in melasma, could be used after treatment seeking to optimize their results through drug delivery.

In a pilot study of photorejuvenation, the effectiveness of the Q-switched Nd:YAG 1064 nm laser (Etherea MX, Vydence) in combination with a cosmeceutical formulation (Hyaxel® 5%, Hydroxyprolisilane C® 4%, DMAE Pidolate® 5%, Nano Vit C® 6%, Matrixyl 3000® 4%) was compared to the use of the laser alone with placebo. The treatment was carried out in four patients, who underwent four laser sessions, with biweekly intervals, followed by the topical application of the formula immediately after the procedure and two more times a day, throughout the study period. In the objective evaluation measured by Focco® equipment, the performance of laser toning combined with drug delivery was superior in the parameters of acne, blemishes, pores, texture, and UV index [5].

Biofilm

Another potential use of photomechanical waves is the permeation increase of antimicrobial agents, promoting drug delivery, for the treatment of biofilms. The biofilm is formed by microbial aggregates that have high resistance to the usual antimicrobial agents, reaching up to 1500 times the normal value. The study by Soukos and collaborators used a single shot of Q-switched ruby laser and got an increase in the permeation depth of methylene blue in biofilms of 75%, thus allowing its photodestruction [20].

Other Uses

A study evaluated the effectiveness of the Q-switched Nd:YAG 1064 nm laser as a drug delivery enhancer in the treatment of onychomycosis. Kim et al. evaluated the effectiveness of the treatment by dividing patients into three groups: group one (treated only with laser); group two (treated with laser and topical antifungal); and group three (treated only with topical antifungal) with monthly laser application, for a total of three or four sessions. The clinical and mycological evaluation demonstrated superiority of the laser treatment combined or not with drug delivery when compared to topical treatment. However, drug delivery seems to be able to prevent reinfection [21].

Noteworthy, studies evaluating the ability of Q-switched laser of promoting drug delivery have been done in organs other than the skin, including its use for transvascular drug delivery which could benefit patients with neoplasms and brain tissue diseases, offering an effective way of crossing the blood-brain barrier [22] and the controlled delivery of active ingredients to the ocular conjunctiva [23].

Illustrated Uses of Q-Switched Lasers in Clinical Practice

Rejuvenation (Fig. 9.3)

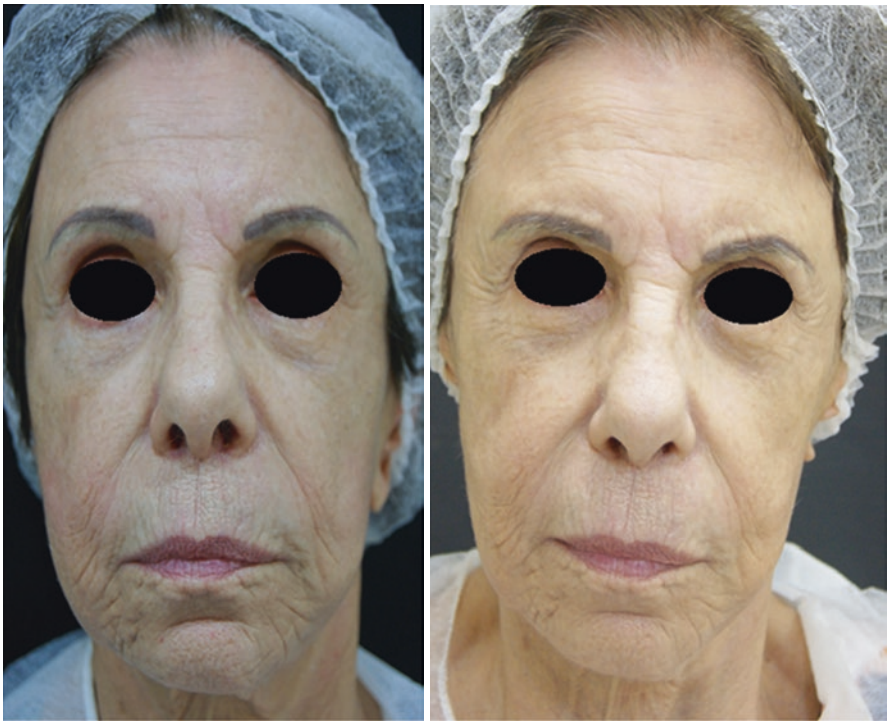

Fig. 9.3 Patient before (left) and after eight sessions of Q-switched Nd:YAG 1064 nm laser (right), with Etherea MX laser, Vydence, spot size 7 mm, 1500 mJ, frequency 5 Hz, followed by drug delivery with Hyaxel 5% + Hidroxiprolisilane C 4% + DMAE 5% + Nano vitamin C 6% + Matrixyl 4% serum

Melasma (Fig. 9.4)

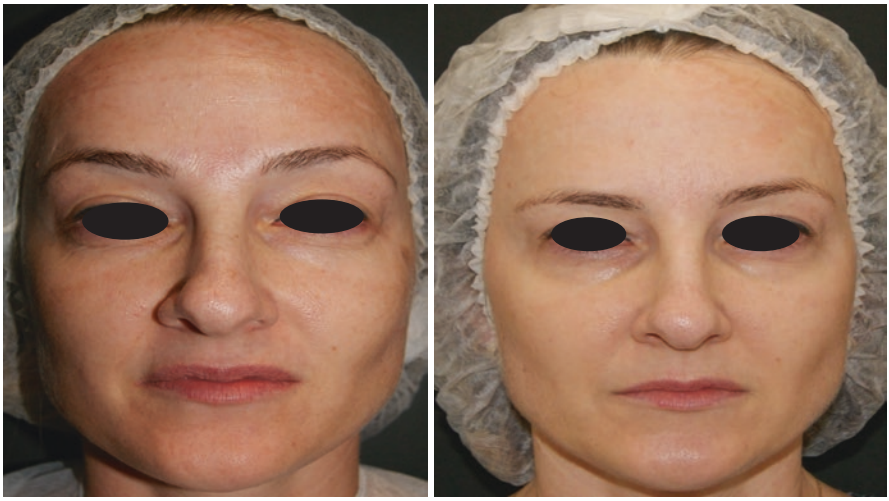

Fig. 9.4 Patient with facial melasma on the face before (left) and after (right) treatment with laser Q-switched Nd:YAG 1064 nm (Etherea MX laser, Vydence), spot size 7 mm, 1200 mJ, frequency 5 Hz, followed by drug delivery with peeling Cisteamina (10 minutes): Cisteamine Hcllemma 5% + Edta 0.2% + Calmred 5% + Atranax 3% + Melyanol 1.5% + Fluid gel lecigel

Conclusion

The choice of a particular method for promoting drug delivery depends on several variables: physical methods, such as those provided by lasers, have the advantage of a reduced risk of chemical and allergic reactions and of not interacting with the desired drug delivery [6]. The current trend, which includes the search for techniques that combine proven efficacy and a lower degree of aggressiveness to promote drug delivery, speaks in favor of using of Q-switched lasers for this purpose [3].

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Chapter 10
Radiofrequency, Infrared, and Other Technologies for Drug Delivery

Paulo Torreão, Luciana Conrado, and Maria Claudia Almeida Issa

Introduction

"Drug delivery" or permeation of drugs through the skin is a treatment method with applicability in several areas of medicine that has aroused great interest of researchers and practicing doctors in the last 10 years. In 1990, the number of articles indexed at PubMed with the keywords "drug delivery" was 1,425; in the year 2000, it was 5,387; and today the number of papers has surpassed 36,000.

The entry of substances that regularly would not penetrate the skin, or would do so in small quantities, is facilitated through various methods that cause some injury to the skin barrier. Through this technique, it is possible to increase the effectiveness of drugs usually topically applied, without exposing the patient to the risks involved in systemic therapy.

The devices used to increase skin permeability include lasers, ablative radiofrequency, and micro-needling.

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Drug Delivery with Fractionated Ablative Laser

The fractionated CO_2 laser (10,600 nm) and the fractionated Er: YAG laser (2940 nm) are the most commonly used lasers for drug delivery through the skin, producing a network of microthermal zones or micro-treatment zones [1]. Each microthermal zone consists of a vaporized cone surrounded by coagulated tissue. Every column of thermal injury is surrounded by intact skin (Fig. 10.1), which facilitates healing when compared to the lesion of the whole epidermis caused by non-fractionated ablative lasers [2–4].

Water is the most abundant substance in the skin and is the target of ablative lasers, mainly Er: YAG (yttrium aluminum garnet – 2.940 nm), Er: YSGG (yttrium scandium gallium garnet – 2.790 nm), and CO_2. The tissues irradiated by these wavelengths pass through three phases as the photon energy is transmitted to water [5–7].

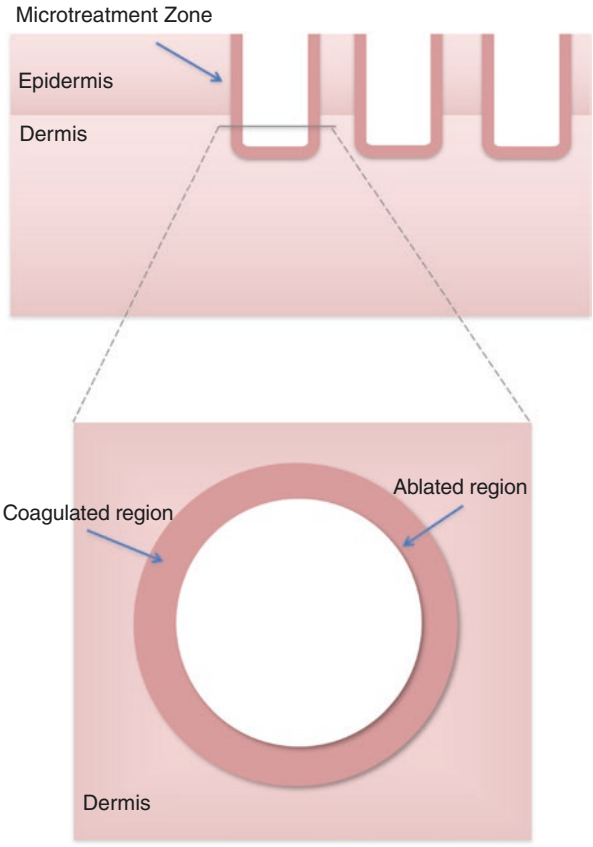

Fig. 10.1 Schematic representation of skin biopsy in vertical and cross section after ablative laser treatment

Phase 1: Direct heating – Heat is transmitted directly and almost restricted to the depth of the light penetration when all photons are entirely absorbed and converted to heat (Fig. 10.3) [5].

The Er: YAG laser penetrates approximately three μm into the skin as it has the highest absorption coefficient for water, and the Er: YSGG laser penetrates ten μm, and it has the intermediate absorption coefficient. The CO_2 laser penetrates 30 μm into the skin with the lowest absorption coefficient for water (Fig. 10.2) [6, 7].

Therefore, the higher the affinity for water, and the higher the absorption coefficients, the lower the penetration of the laser [5–7].

Phase 2: Thermal diffusion (Fig. 10.3) – This occurs when the heat is transmitted to deeper tissues, in addition to the depth limited by the optical absorption coefficient for water and the optical penetration into the tissue: the wider the pulse width, the more evident the result of thermal diffusion, tissue coagulation. However, the smaller the width of the pulse, the less evident is the result of thermal diffusion, as the pulse ends faster than the capacity of the tissue to transmit heat to neighboring structures [6, 7].

The smallest possible coagulation zone for each laser wavelength is limited by the depth of optical penetration, as it is an intrinsic characteristic of the wavelength. However, if we increase the pulse duration, heat is accumulated within the tissue, making the coagulation zone thicker through thermal diffusion, exceeding the range of optical absorption. Therefore, it is not possible to reduce the coagulation zone caused by the wavelength of the laser because it is based on the depth of penetration and optical absorption, but it is possible to increase the coagulation zone through the principle of thermal diffusion, through the increase of pulse [6, 7]. Er:YAG lasers simulate the effect of CO_2 through this method.

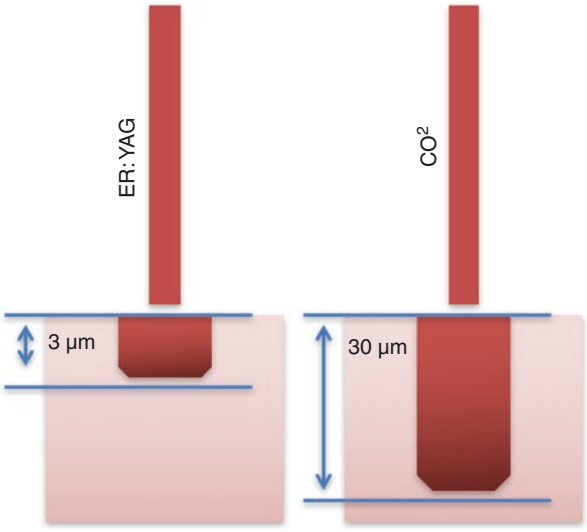

Fig. 10.2 Schematic representation of the penetration depth of the lasers according to wavelength

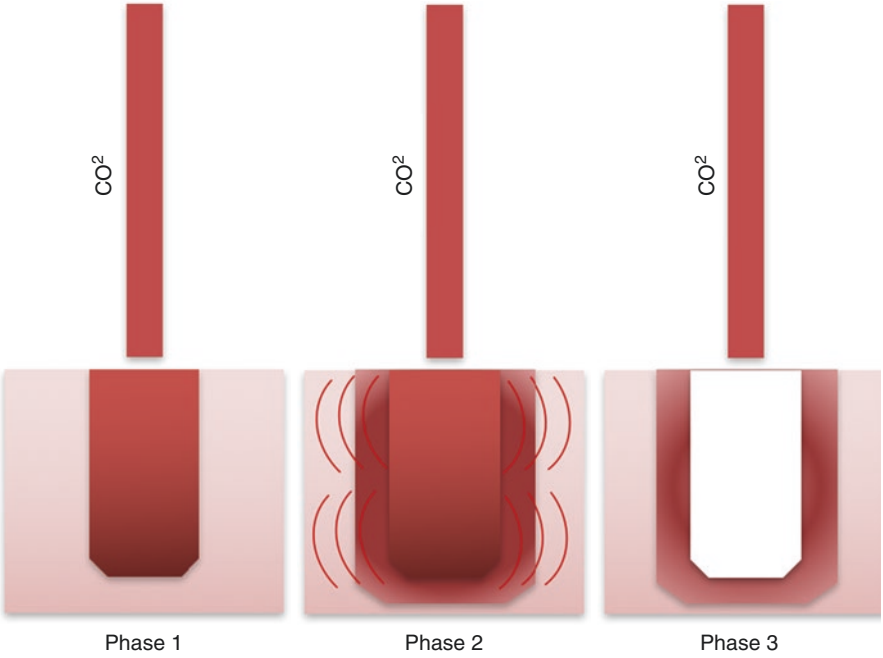

Fig. 10.3 Schematic representation of the three phases the tissue passes through until the ablation is reached, once irradiated by laser. Phase 1, optical penetration according to the limit established by the wavelength and optical absorption coefficient of the tissue; Phase 2, thermal diffusion inducing coagulation; Phase 3, ablation of the most central part of the tissue with extrusion of the material

Phase 3: Tissue vaporization occurs when the upper part of the tissue near the surface is heated to a point where ablation occurs and the material is extruded, leaving a small hole in the surface of the skin, followed by coagulated tissue around it (Fig. 10.3) [6].

Drug Delivery with Micro-Needle

The devices used for the micro-needling, both in the form of stamps and rollers, produce in an analogous way to ablative lasers, a network of injury columns in the skin, alternated with healthy skin. However, this modality does not coagulate the vessels affected by the ablation of the needle, which can generate a counterflow of plasma and blood, making the entry of substances difficult. For this reason, in general, short needles (0.5–1.5 mm) are used to prevent bleeding or local exudation [8–10].

Drug Delivery with Fractionated Radiofrequency

Radiofrequency (RF) devices do not use light but electromagnetic energy (radiofrequency waves) transformed into thermal energy. RF ablates the skin surface ionizing oxygen, when there is a thin layer (space) between the RF tip and the skin, producing micro-sparks (microplasma) that open up the tissue. These micro-sparks create networked microchannels in a manner analogous to the other technologies. As it is a thermal ablative method, coagulation of the skin occurs, avoiding the contraflow of blood [11].

Drug Delivery with Infrared and Near-Infrared

Infrared drug delivery is a very new modality in dermatology, and it is still in very early stages. The mechanism of action differs from the conventional drug delivery model described above with the fractionated ablative methods. In this technique, wavelengths between 400 and 2500 nm are used to penetrate deeply into the tissues and release heat. Specific materials such as carbon nanotubes, graphene oxide, polyethylene glycol microstructures, gold nanocapsules, and liposomes are used to anchor the desired drug in the skin before being irradiated. Through this method, the anchored drug is offered in a systemic way (oral or venous). After reaching the target tissue, it is released or activated locally and controlled with irradiation. Treatments have been described mainly in the field of invasive and metastatic cancer, where other therapies are ineffective in reducing the systemic effects of chemotherapy [12, 13].

Drugs Used for Drug Delivery

Several drugs and cosmeceuticals have been described for use in drug delivery (Table 10.1). Among them, the most studied are MAL, ALA, 5-FU to treat the cancer field, and preneoplastic lesions with positive results. Triamcinolone was also used to treat hypertrophic scars and alopecia areata. Methotrexate was used for psoriasis, lidocaine for anesthetic purposes, vitamin C, and ferulic acid for rejuvenating goals [3].

Regarding the excipient used to retain the active ingredients, Olesen et al. [14] demonstrated that liquid-based vehicles were more efficient in filling the channels created by ablative lasers than gel and cream vehicles, in that order.

A topic that divides the opinion of experts on the subject concerns the use of injectable substances versus non-injectable, or sterile versus nonsterile. However, there is no scientific evidence at the moment to clarify the best approach.

Table 10.1 Drugs and their clinical indications for drug delivery

Indication	Possible drugs
Photoaging	Retinoic acid (0.025–0.005%) Hyaluronic acid 0.1–1%. Vitamin C 5–10% Ferulic acid 0,5%
Melasma	Hydroquinone 4% Phytic and kojic acid 2% Tranexamic acid 5% Ferulic acid 0,5%
Acne scars	Retinoic acid (0.025–0.005%)
Scars	Retinoic acid (0.025–0.005%) Hyaluronic acid 0.1–1%. Vitamin C 5 10% Triamcinolone acetonide 10 mg/ml
Stretch marks	Retinoic acid (0.025–0.005%) Hyaluronic acid 0.1–1%. Vitamin C 5–10%
Alopecia areata	Triamcinolone acetonide 10–20 mg/ml
Hypertrophic scars	Triamcinolone acetonide 10–40 mg/ml
Actinic keratosis	ALA, MAL, 5 FU, ingenol

Relationship Between Drugs' Physicochemical Properties and the Permeation into the Channel After Fractionated Ablative Methods

Hydro/Lipophilicity

The available data on the best laser energies settings and the best depth of the channel for drug delivery into the skin are somewhat contradictory. However, there is evidence that for hydrophilic and slightly lipophilic molecules, the absorption of drugs was dependent on the depth of the channel. In contrast, lipophilic drugs showed an independent uptake to the depth of the channel [15, 16].

Density and Molecular Weight

Haak et al. [17] described the impact of laser treatment density (% of skin occupied by channels) and molecular weight of the substances for drug delivery using a fractionated CO_2 laser. Fractionated ablative treatment substantially increased the transcutaneous delivery of polyethylene glycols (PEGs), at a molecular weight ranging

from 240 to 4300 Da. Increasing the laser density by 1–20% resulted in generally increased intra- and transdermal delivery. However, for densities higher than 1%, there was a reduction in delivery when evaluated separately by each channel. Mass spectrometry indicated that larger molecules have higher intracutaneous retention than transcutaneous penetration.

Wavelength and Parameters

Taudorf et al. [4] conducted an animal ex vivo skin study with a 2940 nm laser to establish the impact of laser parameters, staking, and effects on tissue. It was observed that low pulse energy and high repetition rate required a lot of staking of pulses at the same point to induce ablation. The ablation depth was also affected not only by the total energy provided by the pulses' stacking but also by varying pulse energy, pulse repetition rate, and pulse duration. The low pulse repetition rate (Hz) and the reduced number of pulses stacked are important to avoid the progressive accumulation of residual heat, allowing exposed tissue to cool and the ablation channel to be evacuated between pulses. The authors also discussed the advantage of using the Er: YAG (2.940) against CO_2 laser, due to the interference of the coagulation zone in drug permeation. Although the importance of the coagulation zone is not fully established, a thick coagulation zone could represent a significant barrier to molecules' delivery [4].

Life Cycle of the Ablation Channel

Recently it was observed by Banzhaf et al. [18] that 100% of the channels created by a fractionated CO_2 laser were kept open in the first 30 minutes after the intervention. From this point on, there was a gradual decrease in the percentage of channels opened, with a substantial reduction after 6 hours. Any data is currently available on other lasers and their respective closure timings.

Medication and Micro-Needles

Some authors advocate drug application before needling; others consider it better to apply it after needling. Kapsok Li et al. demonstrated that the application of the drug after the procedure induces greater penetration [19]. Kalluri et al. [20] showed, using transepidermal water loss measure (TEWL), that the ablation channels remain open for about 4 hours. They reported that substances' capability to pass through the channels was related to the number of passes and the size of the needle. It was found that the needle size did not interfere with the result, but the higher the number of

passes, the higher the TEWL [20]. Sasaki et al. evaluated with tattoo ink applied at several moments after the needling that the best moment for permeation into the channels occurred between 5 and 30 minutes after the opening [21]. In a study with hydrophilic drugs, it was demonstrated that the transdermal penetration of the evaluated substances was eight times higher in the treated skin than in healthy skin [22].

Therapeutic Indications

Photodynamic Therapy

The use of ablative lasers [8] and micro-needle technique [23–25] before the application of methyl aminolevulinate (MAL) for photodynamic therapy (TFD or PDT) has already been documented.

A recent study compared the clinical effects induced by MAL-PDT with red light versus MAL-PDT with red light associated with TED using fractionated ablative radiofrequency. The results showed that, even reducing the incubation time of the photosensitizing agent (MAL), from 3 hours to 1 hour, an improvement in actinic keratosis and skin texture was observed. "Drug delivery + PDT" was more effective in reducing actinic keratosis lesions in the forearms than PDT alone. Besides, the improvement in texture and pigmentation was remarkable on the side treated with drug delivery + PDT [11].

Scars

Hypertrophic scars and keloids are disorders of the healing process in individuals predisposed, secondary to different types of dermis lesions such as inflammation, surgery, burns, and trauma. Despite growing knowledge in wound repair and collagen metabolism, keloid scars remain a challenge for dermatologists and plastic surgeons. Clinically, hypertrophic scars are limited to the original site of the lesion, while the keloids go beyond the wound limit and reach the adjacent skin. Hypertrophic scars appear 4 weeks after the triggering event, grow intensely for a few months, and then regress. In keloids, collagen production is 20 times higher than healthy healing and rarely disappears spontaneously. It can be challenging to distinguish them in the early growth phase [26].

The intralesional application of steroids is the first choice for hypertrophic scars. Triamcinolone acetonide has a powerful anti-inflammatory action and is a good option. Its mechanism of action involves fibroblasts' proliferation inhibition and collagen synthesis. It also increases collagenase production and reduces collagenase inhibitors. It should be applied every 2–6 weeks until the clinical improvement of the lesion or the appearance of local side effects prohibiting its use. The use of

intralesional corticosteroids is painful, and the distribution is not homogeneous [27, 28].

Garg et al. demonstrated that CO_2 laser alone was insufficient to permanently treat keloids, requiring an intralesional application of triamcinolone every 3–4 weeks for 6 months after ablation [29].

Issa et al. performed a study with transepidermal application of fractional radiofrequency plus triamcinolone associated with impact ultrasound for the treatment of hypertrophic scars. The results showed improvement or complete resolution of hypertrophic scars with excellent aesthetic result. This technique was also considered less painful than regular injections. It is worth noting that in another unpublished study, using the same method for the treatment of keloids, the same effect was not observed [30].

The authors also report the use of tretinoin 0.05% drug delivery in cream for non-hypertrophic post-surgical scars (Fig. 10.4).

Atrophic Stretch Marks

Atrophic stretch marks are very common and easily recognized dermatosis, which rarely causes significant medical problems but is a frequent complaint. The origin of stretch marks is not well known. There are several therapeutic modalities, but none of them is considered very effective, and no single therapy is 100% resolutive. Early stretch marks respond better to treatments (topical tretinoin, subcision, microneedling, and lasers) than old stretch marks [31, 32].

A case report about drug delivery, using 0.05% tretinoin in cream, after fractionated ablative radiofrequency showed good results for atrophic white stretch marks, mainly located on the breast. Comparing results when treating white striae in the abdomen with tretinoin 0.05% cream after fractionated ablative RF or fractionated ablative radiofrequency isolated, the association with tretinoin showed better results [33].

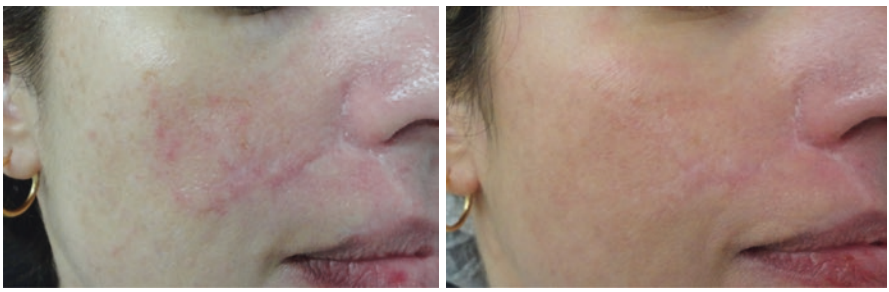

Fig. 10.4 Before and after one session of fractionated ablative radiofrequency and drug delivery of tretinoin cream 0.05%

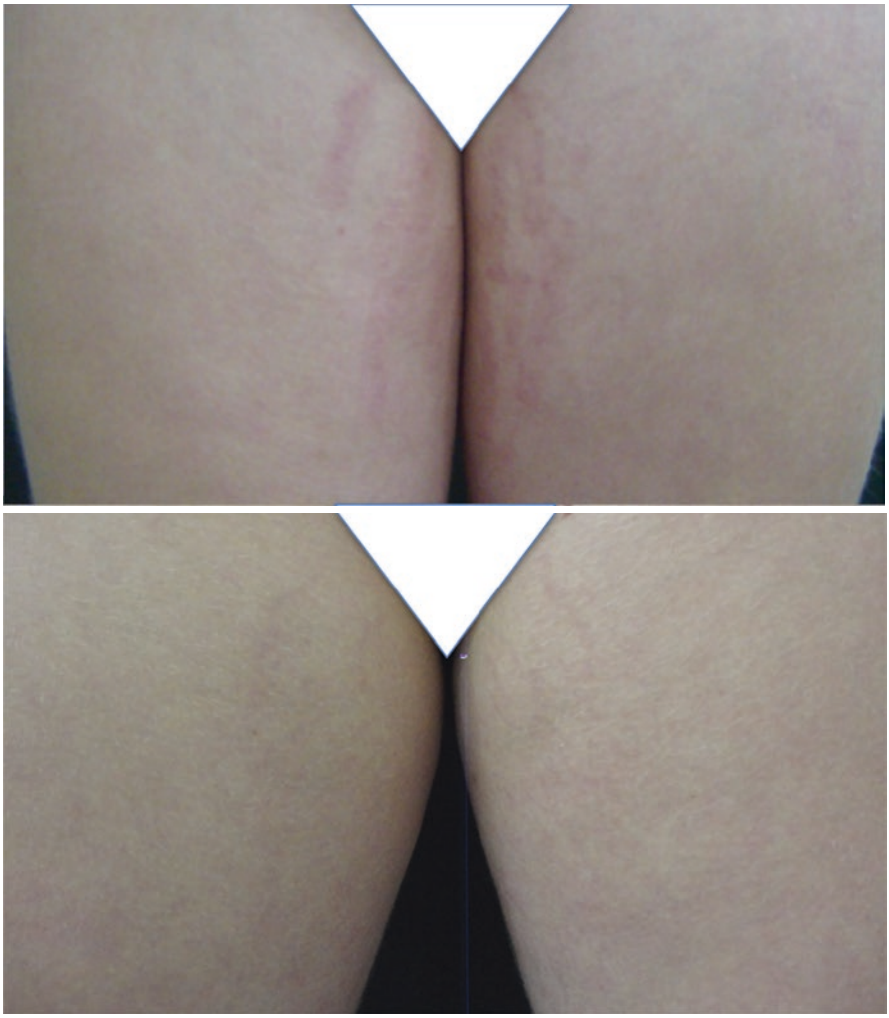

Fig. 10.5 Before and after three sessions of CO_2 laser and drug delivery of tretinoin cream 0.05%

The authors also have good experience in treating red stretch marks and white stretch marks with drug delivery of tretinoin 0.05% cream after CO_2 laser (Fig. 10.5).

Alopecia Areata

Alopecia areata (AA) is the most common cause of non-scarring alopecia. It is an autoimmune disease with a genetic predisposition. Environmental and ethnic factors seem to be involved. It commonly presents itself as oval or circular areas

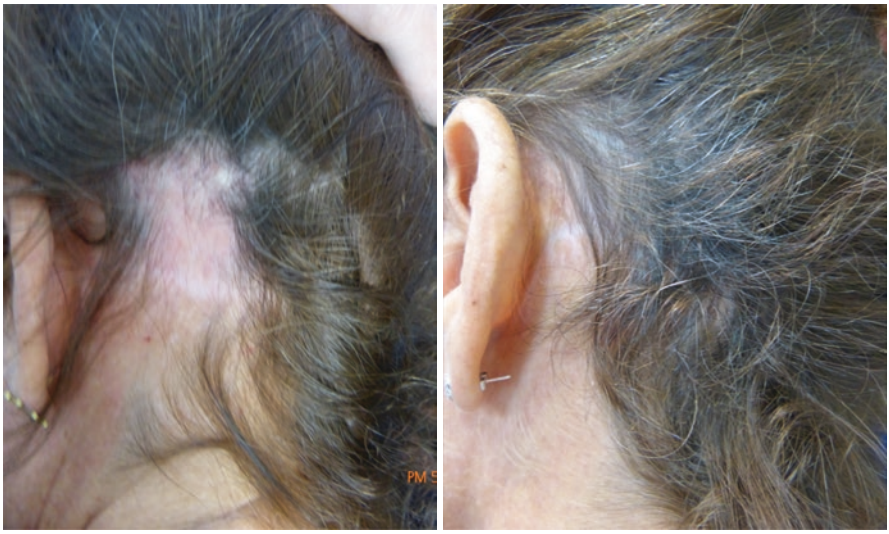

Fig. 10.6 After one session of CO_2 laser and drug delivery of triamcinolone suspension 20 mg/ml

without hair. Steroids are widely used to treat AA, such as intralesional triamcinolone. It is a useful but painful method limited to the area of infiltration [34]. Issa et al. [35] reported an excellent clinical improvement of AA cases, which were treated with fractionated ablative methods (CO_2 laser or radiofrequency) associated with triamcinolone (Fig. 10.6). The authors reported that triamcinolone, previously treated with fractionated ablative techniques, was topically applied to the area, showed homogeneous distribution, promoted alopecia area recovery, and reduced the pain of the intralesional injections.

Photoaging and Melasma

Medicines used for the treatment of clinical signs of photoaging and melasma include tretinoin, vitamin C, ferulic acid, hydroquinone, glycolic acid, and several others [3].

In the case of melasma, the CO_2 laser should be used with very low energy, aiming to produce microchannels on the skin surface. It is possible to see good results with 4% hydroquinone cream without post-inflammatory hyperpigmentation (Fig. 10.7).

In a split-face study for photodamaged skin, CE Ferulic formula (L'oreal-SkinCeuticals) was evaluated after fractionated ablative laser decreasing postoperative recovery time and increasing neocollagenesis on the side treated with drug delivery [36, 37].

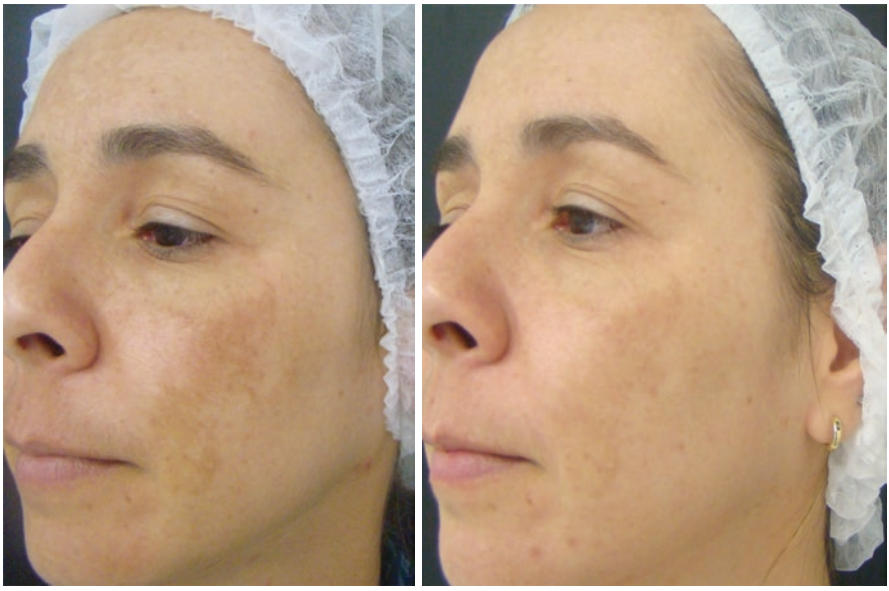

Fig. 10.7 Before and after three sessions of CO_2 Laser 10 mJ/pixel (roller) – Alma Lasers and application of hydroquinone 5% cream associated with ultrasound impact

Application Protocol and Instructions

Prophylaxis with antivirals is advised with the usual dose of treatment, starting 2 days before the procedure, regardless of the history of herpetic infection, and maintained for 5–7 days or until healing.

The skin to be treated should be cleaned using a soap-free cleansing lotion and then with chlorhexidine solution. The fractionated ablative method is used on dry skin, with subsequent topical application of the chosen drug according to the pathology or condition to be treated.

The drugs can be in cream, solution, or serum vehicle, with the same concentrations of the products used topically at home, without the need for high concentrations. However, it is worth remembering that some authors have already described the properties of the drugs and their vehicles, as well as the duration the channels remain open according to the wavelength of the lasers and the number of ideal passes.

When possible, the impact ultrasound can be used to push the drug into the dermis through the channels pre-formed by ablative methods, as a “hammer effect” to enhance the permeation of the drug.

Post-procedure instructions include proper hygiene with antiseptic soap, which starts after 6 hours of intervention. The use of repairing moisturizer is advisable, three to five times a day, avoiding the formation of crusts. The patient is advised not to remove any crusts. It is advisable to avoid exposure to the sun over the healing time. Topical photoprotection should be started on the third day. Oral photoprotection can also be indicated, especially in cases of melasma.

Conclusions

By using fractionated ablative methods for "drug delivery," it is possible to achieve a more uniform and convenient application of drugs, as well as a more effective treatment than the use of topical medications or laser alone.

Drug delivery with radiofrequency, lasers (CO_2 and erbium), and needles can promote good results in several dermatoses. Each method has its advantages and disadvantages. Radiofrequency and needling can be used in all phototypes, as they do not cause dyschromia frequently. On the other hand, CO_2 and erbium lasers can bring better results with fewer sessions.

New studies are necessary to find better techniques for certain drugs, vehicles, and molecules. Hydro and liposolubility, concentrations, laser parameters, and lengths of needles still need to be determined.

Regarding the use of infrared, new technologies are being developed to address invasive and metastatic lesions.

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Chapter 11
Drug Delivery in the Treatment of Alopecias

Mariana Andrade Lima and Emerson Andrade Lima

Main Points

- The topical route of drug delivery is fundamental in dermatology.
- It minimizes possible side effects associated with systemic medication use.
- Chemical, physical, and mechanical methods can be used in order to optimize skin penetration of the drug.
- The drug delivery technique can increase the absorption of larger molecules by up to 80%.
- Therapeutic options in addressing alopecia are limited, making it even more important to develop new treatments.
- Drug delivery assisted by lasers and the use of microneedles have been reported in some scientific articles recently as alternative or complementary options in alopecia treatments.

The skin is the largest organ in the human body, and its main function is to be a protective barrier against infectious agents, chemicals, and water loss. Through the capacity of absorption, it can be considered a safe and effective route for the application of

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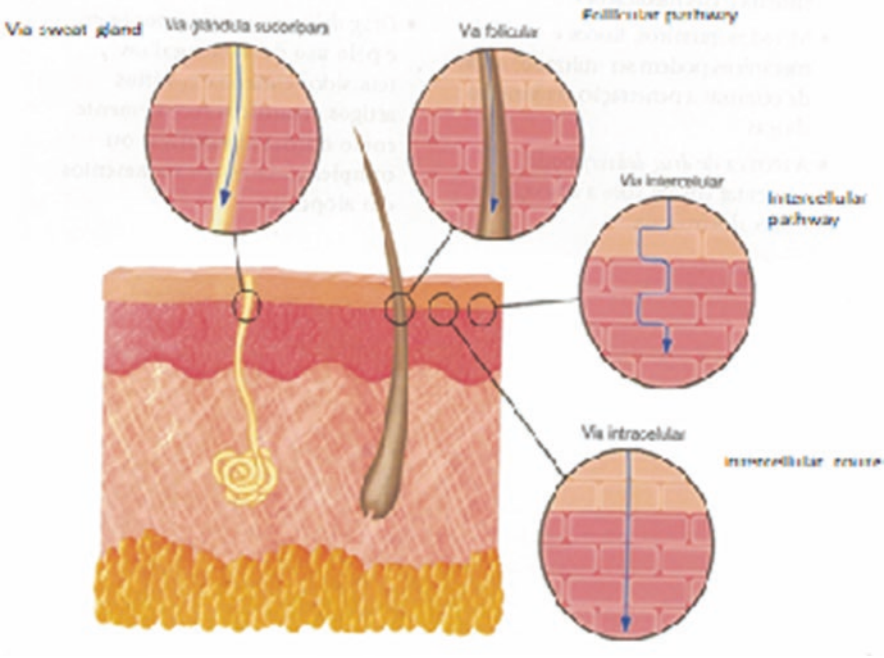

Fig. 11.1 Pathways of penetration of substances into the skin (intracellular, intercellular and follicular)

various drugs. The active ingredients are placed on the surface of the skin and can penetrate transpidermally or through the cutaneous appendages (Fig. 11.1).

As the skin represents an efficient barrier to the penetration of molecules, several chemical and physical methods have been developed to modify the barrier properties of the stratum corneum and increase its permeability.

In order to increase skin permeability and optimize the penetration of substances, several techniques have been used such as ultrasound, iontophoresis, electroporation, microdermabrasion, thermal ablation by lasers, and microneedles. The use of microneedles and lasers has been further studied as complementary techniques in alopecia treatments, either alone or with the addition of drugs.

Physical methods to increase skin permeability include those that destroy the stratum corneum barrier and those that act by external force, pressing the active ingredients in the skin. These techniques provide an increase in the number of substances that can be efficiently transported. In procedures with microneedle devices, conduits are produced in the skin, allowing substances (from small hydrophilic molecules to macromolecules) to penetrate (Fig. 11.2).

The use of microneedles and lasers has been more studied as complementary techniques in alopecia treatments, alone or with the addition of topical medications. In the opinion of the authors, this therapeutic modality should be used as an adjunct method to already establish treatments, in cases of unsatisfactory or nonexistent response to them. There are reports of its applicability in androgenetic alopecia, alopecia areata, and lichen planus pilaris (LPP) not responsive to other approaches.

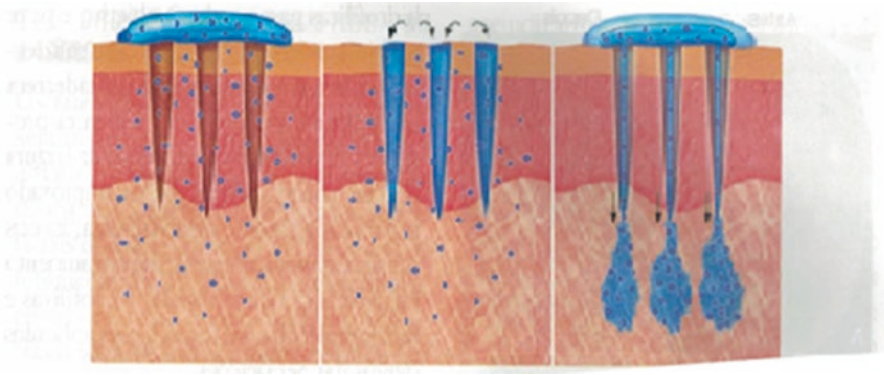

Fig. 11.2 The needles create conducts in the skin allowing the penetration of small hydrophilic molecules and even macromolecules

Medications to be used should be chosen according to the pathology to be treated. With the exception of triamcinolone, the other medications used for drug delivery have not yet passed through the safety and efficacy trials, and little is known about their pharmacodynamics and pharmacokinetics when applied by this route.

Percutaneous Collagen Induction (PCI) and Drug Delivery in the Treatment of Alopecias

Percutaneous collagen induction (PCI) therapy is a method used by dermatologists as a treatment modality for scars and wrinkles. The technique was introduced in the medical literature in 1997, when a tattoo machine without pigment was used to treat facial scars.

This technique produces thousands of controlled micro-perforations in the papillary and reticular dermis. The objective is to perform a mechanical stimulation of the dermis with minimal damage to the epidermis, thus promoting the formation of collagen and increasing angiogenesis. Dermal vasodilatation and migration of keratinocytes occur immediately, resulting in the release of cytokines such as interleukin-1, interleukin-8, interleukin-6, TNF-α, and GM-CSF.

The application of microneedles allows the creation of an accessible means of transport of macromolecules and other hydrophilic substances to the skin. The goal is to generate multiple micro-punctures, long enough to reach the dermis and trigger an inflammatory stimulus. The technique promotes the rupture of the stratum corneum from the width of two to four cells, an effect proven microscopically by the visualization of the channels. Consequently, there is an increase in the permeation of hydrophilic molecules and macromolecules of the formulations applied after the perforations.

Microchannels facilitate drug delivery efficiently and can increase the absorption of larger molecules by up to 80% [1–4].

Several studies have demonstrated the importance of PCI in cell stimulation and growth factor production, showing an increased expression of genes related to hair growth stimulation [5–7].

The use of topical minoxidil associated with microneedles in the treatment of androgenetic alopecia has shown that faster repilation occurs, in addition to improved hair texture and shine in this treated group when compared to the use of minoxidil alone [8].

The efficacy of PCI has been demonstrated in combination with the use of triamcinolone to stimulate hair growth in the patients with alopecia areata. The mechanism of action of microneedling is to increase the vascularization of hair follicles, and the microlesions created induce hair growth through the release of growth factors and stimulate the expression of Wnt proteins [5–7, 9, 10].

Laser-Assisted Drug Delivery in the Treatment of Alopecias

Lasers promote drug delivery by the following mechanisms: non-ablative resurfacing, tissue ablation with removal of the stratum corneum and more superficial layers of the epidermis, and by the action of photomechanical waves, resulting from the conversion of light energy into mechanical energy. The effectiveness of the laser-assisted drug delivery technique is being investigated for several drugs.

Ablative lasers, especially Er:YAG 2940 nm, which operates in the infrared range and has water as the target chromophore, are the most used with the aim of facilitating drug delivery through the creation of thermal micro-zones (TMZ). TMZ are tissue ablation columns, surrounded by clotting tissue, which penetrate the stratum corneum and allow direct access of the drugs to the lower layers. TMZ can be tailored by the parameters "density" (amount of micropores per certain area) and "depth," controlling the fluency used. The degree of ablation and the thickness of the coagulation columns adjacent to the TMZ can be determined by the type of wave and the pulse duration used. Very thick and very deep columns may impair respectively the diffusion of the medication to the surrounding tissues and the permanence of the substances in the dermis.

Some cases of the use of the non-ablative fractional laser Er:YAG 1340 nm in association with medication permeation have also been reported [11]. In the publication, the authors present a case of a patient with androgenetic alopecia treated with six sessions of Er:YAG 1340 nm laser associated with drug delivery with minoxidil. They emphasize that the permeation of the drug can be increased by at least 6.8 times with the technique, being this effect ephemeral, lasting 15 to 30 minutes (Fig. 11.3).

MMP® (Microinfusion of Drugs into the Skin) in the Treatment of Alopecias

With recent description in the literature by Arbache et al., the technique of MMP® (microinfusion of drugs into the skin) promotes the infusion of medications associated with the microneedle procedure, using tattoo machines. It is worth pointing out

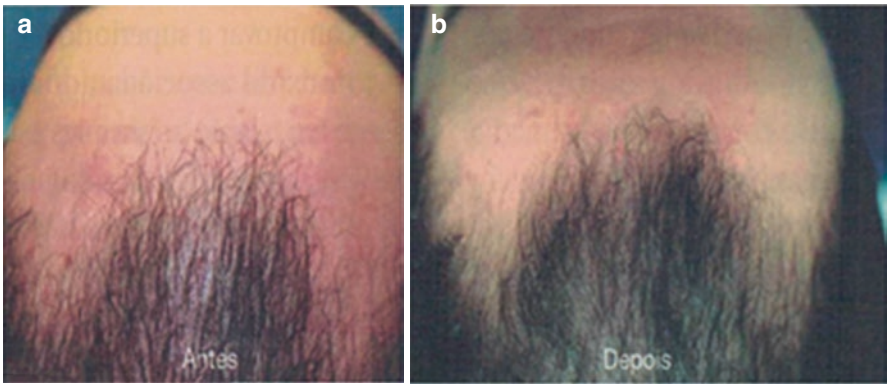

Fig. 11.3 Androgenetic alopecia before (**a**) and after treatment with six sessions of Er-YAG 1340 nm with drug delivery of minoxidil (**b**)

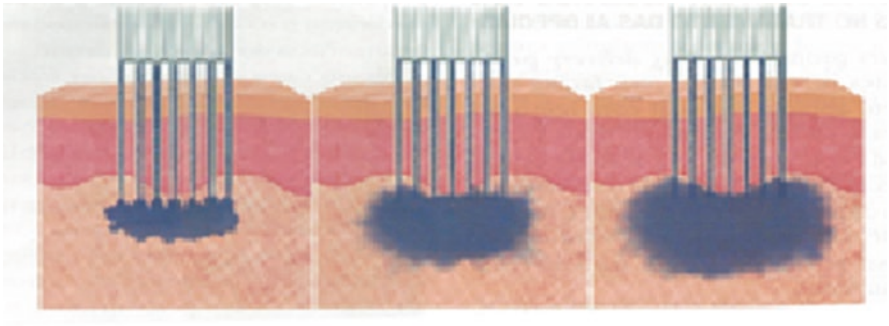

Fig. 11.4 Illustration of ink injection into the skin to be slowly absorbed by "infusion" process

that the orifices produced by the machine are similar to that created by rollers, promoting release of growth factors, activation of stem cells, and overexpression of genes related to follicle growth.

The procedure is performed in a manner analogous to professional dermopigmentation. Small motors drive rotating axes, moving cartridges, or needle rods. The cartridges are made up of a variable set of microneedles of fine diameter. At each "up and down" cycle, the needles pierce the epidermis and insert the medication simultaneously. The medication injected in excess into the dermis is eliminated by the same entrance hole, being slowly absorbed by a process called "infusion," which differs from the conventional injection process through syringes [12].

The theoretical basis that justifies MMP® is the concept that a drug injected into the dermis is released more slowly, maintaining a micro-deposit that allows its action for longer periods. This would enable the use of smaller doses to achieve the desired therapeutic effect on the target tissue (Fig. 11.4).

In 2016, Contin reported two cases of male androgenetic alopecia treated using a tattoo device using the MMP® technique. In one patient, four microneedling sessions (1.5 mm) were performed with drug delivery of a 0.5% sterile minoxidil

solution. The second patient underwent three similar procedures, but without the addition of medications. The author reports cosmetically satisfactory response in both patients but concludes that more evidence is needed to prove the superiority of minoxidil injection associated with microneedling over the simple topical use of medication, microneedling alone, and the effectiveness of the MMP® technique (Fig. 11.5).

Barletta et al. described two cases of alopecia areata successfully treated with triamcinolone acetonide using the MMP® technique. Both patients had evident

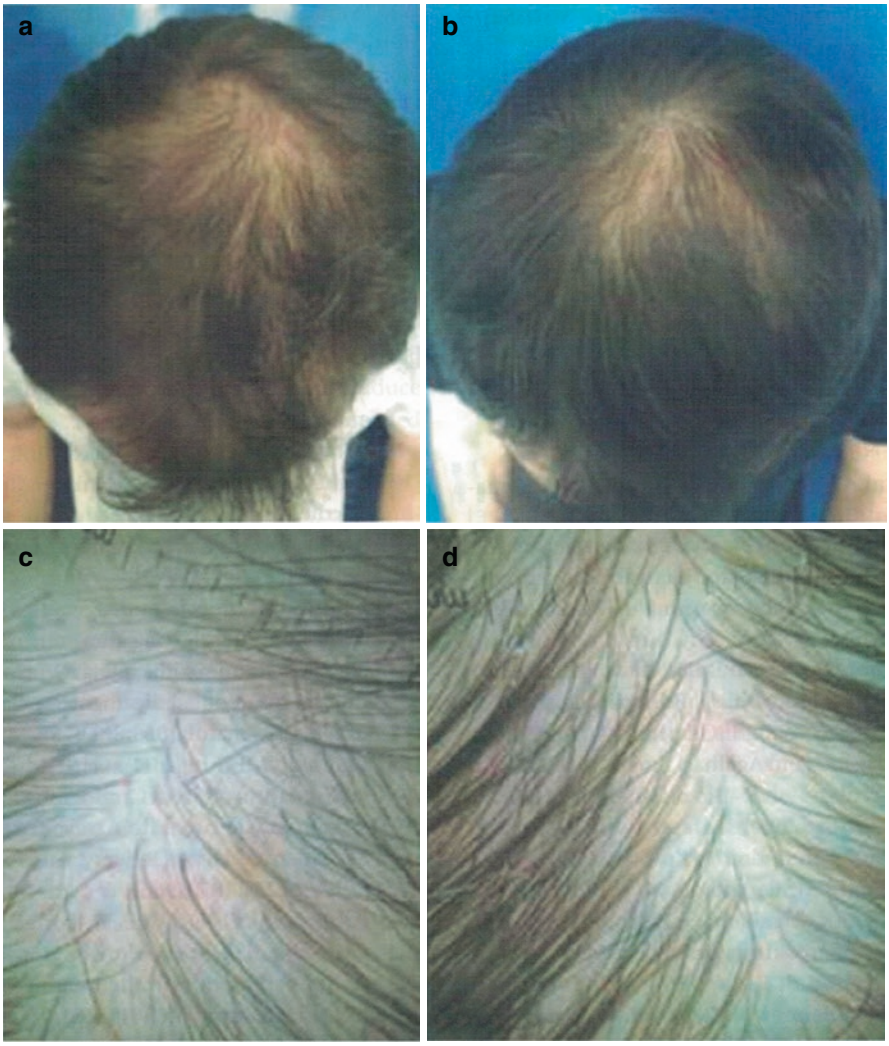

Fig. 11.5 Androgenetic alopecia treated with tattoo device and minoxidil infusion. Before treatment (**a** and **c**), after treatment (**b** and **d**)

improvement, including a partial regrowth of an ophiasic area in one of the patients, a specific anatomical region notably resistant to treatments. The authors considered MMP® as a promising and safe therapeutic option but stressed the need of standardized protocols to confirm their findings.

Conclusion

The cases published so far have used a wide range of medications, sometimes in combinations known as "blends" or "mélanges," mixing medications like minoxidil, finasteride, dutasteride, vitamin complexes, growth factors, corticoids, and even platelet-rich plasma (PRP). Few randomized clinical studies have been published, and further research is needed to better elucidate the indications and particularly the ideal characteristics and safety of the substances to be applied. It is important to emphasize that each drug has its own pharmacokinetics and the ideal dose for each of the drugs used by this route has not yet been determined.

The use of sterile products is a controversial topic, as contamination with microorganisms located on the skin surface may occur even after correct antisepsis of the treated area.

The authors consider the drug delivery technique extremely promising, and it can be employed as a complementary method for the most established modalities of treatment for alopecias. It should not be indicated as the first and only therapeutic choice but as an adjunct to conventional treatments.

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Chapter 12
Digital Microneedling and Drug Delivery

Alexandre de Almeida Filippo, Bruna Dal Bello, Paula Regazzi de Gusmão, and Gustavo Robertson Filippo

The infusion of medications directly into the skin refers to the concepts of mesotherapy proposed by Pistor in the mid-1950s. Dermal or subcutaneous injection of active ingredients, especially when associated with microneedling procedures, is able to stimulate the tissue by the action of both the puncture and the drugs.

Despite the lack of methodological standardization for the infusion of medications into the skin, there are substances banned for intradermal or subcutaneous use, such as those with an alcoholic or oily base, due to the risk of cutaneous necrosis.

Intradermal application provides a greater interface of the applied product with the target receptors since the systemic absorption is lower in dermal application. On the other hand, in certain indications such as for lipolysis, it is desirable that the product reaches the subcutaneous tissue to exert its action. The fragmentation of the total amount of the product applied in a greater number of punctures also contributes to increase the contact of the active ingredient injected with the target tissue, thus increasing the therapeutic effect of the medication.

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Recently, transdermal drug delivery systems with microneedles have been developed for the infusion of lipophilic, hydrophilic, and macromolecule active ingredient directly at their site of action.

The system known as digital drug delivery consists of an electronic multi-needle injector, which accurately controls the injection depth and the dose of the drug. Its main characteristics are the possibility of using active ingredients of different densities in many anatomical sites, from the epidermis to the hypodermis, with total control of the infusion volume and a low cost. In addition, it is an innovative technique, with a short recovery time, that does not prevent the patient from performing daily activities and that can be applied with minimal risk of adverse effects compared to other techniques.

It features a handpiece with adjustable syringe holder, where the device is attached with microneedles. Each shot is made when the trigger is pressed, and the balanced pressure in the microneedles allows the infusion to be homogeneous throughout the treated area.

In addition, the device has a vacuum system, with adjustable strength, installed in the main injection device and connected to the handpiece by a tube. The mechanical vacuum stimulus triggers the release of opiate substances in the brain (endorphins, serotonin, and enkephalins) that act as pain-inhibiting neurotransmitters in the central nervous system. Vacuum also separates the skin from the subcutaneous layer, minimizing potential complications such as bruising and embolism, caused by the intravascular injections of substances.

The injector itself stimulates neocollagenesis through the skin puncture and the consequent increase in the collagen expression and release of platelet-derived, endothelial and epidermal growth factors.

After recent years of progress, digital microneedling has become one of the main drug delivery enhancement techniques. As is evident in the ongoing clinical trials of a wide variety of drugs for various clinical conditions, including rejuvenation, skin lightening, hair treatment, application of botulinum toxin and hyaluronic acid, flaccidity, localized fat, gynoid lipodystrophy, and treatment of diseases, such as vitiligo and psoriasis, the prospect is that the digital drug delivery system will establish itself as the gold standard in active ingredients transdermal delivery.

Most active ingredients used in digital microneedle-assisted drug delivery are obtained by sterile manipulation. Substances can be handled alone or in mixtures composed of synergistic substances for each therapeutic indication.

Active Ingredients for Microneedle-Assisted Drug Delivery

Tranexamic Acid

Tranexamic acid is an antifibrinolytic medication that inhibits plasminogen activation in plasmin. By doing so, it interferes with the inflammatory cascade induced by ultraviolet radiation, which occurs in melasma, leading to inhibition of

melanogenesis. It can be used to treat melasma both systemically and topically, intradermally and transepidermally. The intradermal route is more effective than the topical or transepidermal one and as effective as the systemic route, with the benefit of having fewer side effects and/or contraindications related to prothrombotic repercussions. In addition, there seems to be less relapses after treatment with tranexamic acid by the intradermal route than by the oral one.

For intradermal use, it is recommended to use tranexamic acid in concentration of 4 mg/ml, maximum of 2 ml per session, in monthly applications in the affected area for approximately 12 months. It is important to note that the initial response of this medication in melasma is poor and, regardless of the route used, the benefit will start to be seen after 4 weeks from the beginning of the treatment.

Hyaluronic Acid

Hyaluronic acid, alone or in multicomponent formulas, is a key element for the treatment of skin aging. When applied intradermally, besides its hydration capacity, it can stimulate fibroblasts to produce, in the treated areas, a greater amount of type I collagen, elastin, and endogenous hyaluronic acid. This improves the skin's texture, elasticity, and thickness. As it has an indication for intradermal application, better results are obtained when small volumes are infused by injection.

Vitamins, Coenzymes, Antioxidants, Amino Acids and Minerals

These are widely used in multicomponent formulations to provide a favorable microenvironment so other substances may have their potential enhanced. For example, by combining vitamins, coenzymes, amino acids, and minerals with hyaluronic acid, the fibroblasts will have all the necessary substrates to increase the biosynthesis of collagen, elastin, etc. These substances are also commonly associated with minoxidil, finasteride, dutasteride, etc.

Vitamins make up most of the coenzymes (catalysts for biochemical reactions) and cellular antioxidants. The most used are the B vitamins (thiamine, riboflavin, nicotinamide, pantothenic acid, pyridoxine, biotin, folic acid, cyanocobalamin, and inositol), vitamin C (ascorbic acid), vitamin A (retinol), and vitamin E (tocopherol). The main minerals used as adjuvants in multicomponent formulas are calcium, phosphorus, and magnesium which, respectively, regulate cellular homeostasis, compose biological membranes, and regulate enzymatic reactions.

Silanol Salicylate

It is a substance composed of organic silicon which can stimulate the synthesis of collagen and elastic fibers when applied intradermally. It has good indication in the treatment of photoaging, rhytids, and atrophic scars.

Dutasteride

It is an approved oral dual inhibitor of 5-alpha-reductase for benign prostatic hyperplasia. Although off-label, it is also effective in the treatment of androgenetic alopecia. Despite the abundant vascularization of the scalp, the intradermal application of the medication in this area does not seem to lead to important systemic absorption, minimizing the occurrence of the dreaded side effects associated with the substance (decreased libido and erectile/ejaculatory dysfunction). Local application can increase both capillary density and stem diameter.

Concentrations ranging from 0.005% to 0.05% are used in quantities of 1 to 2 ml per session. It can also be administered in multicomponent formulas combined with nonspecific hair growth promoters (usually dexpanthenol, biotin, pyridoxine, etc.). It can be applied at weekly intervals, but due to its long half-life (approximately 4 weeks), longer intervals, e.g., quarterly, can be used without prejudice to the results.

Finasteride

It is also a 5-alpha-reductase inhibitor widely used in the treatment of androgenetic alopecia. Due to the shorter half-life (approximately 8 hours), it should be used in weekly or fortnightly applications. As with dutasteride, intradermal applications of 0.05% finasteride have a low incidence of systemic side effects.

Minoxidil

It is a piperidinopyrimidine derivative and a potent vasodilator initially developed as an antihypertensive. The exact mechanism of action by which it stimulates hair growth has not yet been fully elucidated, but it is known for its capacity of prolonging the anagen capillary phase. The delivery of the drug close to the follicle in the dermis enhances its effect. For intradermal applications, concentrations between 0.5% and 2% are used, initially, in weekly applications that can be spaced further apart with the progression of the treatment. It is suggested that 0.1 ml of the solution can be applied to each puncture.

Bleomycin Sulfate

It is an antineoplastic that inhibits collagen synthesis by fibroblasts. It is used to treat keloids, hypertrophic scars, and viral warts in intralesional or transepidermal applications. It is commercially provided as a lyophilized powder containing 15 units of the active ingredient.

It can be diluted in 10 ml of sterile saline solution, resulting in a concentration of 1.5 IU/ml. Multiple intralesional injections of 0.1 ml (0.15 IU) each are recommended, respecting the limit of 0.4 ml/cm^2 and a maximum of 3.5 ml per session. The sessions can be repeated monthly according to clinical response. Usually, an average of four sessions are needed.

Platelet-Rich Plasma (PRP)

Autologous platelet-rich plasma is a by-product of centrifugation of the patient's own blood. Although it is still considered experimental by the Federal Council of Medicine, it has had more and more clinical indications and evidences of efficacy in many publications. Platelet alpha granules (present in large quantities in PRP), when activated, release growth factors capable of stimulating cell proliferation and differentiation, especially of fibroblasts. These fibroblasts promote the increase of dermal collagen, improving aging skin. Some of the growth factors released seem to have the ability to inhibit melanogenesis, and, therefore, the perceived improvement in melanosis and melasma after treatment with PRP is justified. By promoting tissue repair, neoangiogenesis, and epithelization, PRP is also useful in the treatment of atrophic scars such as stretch marks, acne scars, and surgical scars.

Once prepared and activated, the platelet-rich plasma should be applied quickly so that there is no clotting (approximately 10 minutes). It is recommended to inject approximately 0.1 ml per puncture distant from each other in 1 cm. The depth of application is intradermal (approximately 1.5–2 mm).

Deoxycholic Acid/Sodium Deoxycholate

It is a lipolytic substance used to treat localized fat, especially on the face and neck. It acts as a detergent, disintegrating the adipocyte cell membrane. Although it can also act on cell membranes of keratinocytes, fibroblasts, and skeletal muscle fibers, there seems to be some mechanism (not yet well established) that minimizes/neutralizes the effects of deoxycholic acid in these structures. It should be applied to the subcutaneous tissue in larger doses and with fewer stitches than intradermal applications of active ingredients.

There are commercial treatments designed with deoxycholic acid such as *Kybella*® (Allergan), approved by the FDA in 2015, but, so far, not yet available in Brazil. The product is indicated for the treatment of submental fat in adults. According to the manufacturer, a maximum of 50 punctures spaced 1 cm apart, with an infusion of 0.2 ml in each one, should be performed. A maximum of six sessions with monthly intervals are recommended.

The side effects associated with the use of deoxycholic acid are generally well tolerated and represented by erythema, edema, and ecchymosis. Although rare, there are reports of late complications with necrobiosis in the reticular dermis, necrosis of adnexal glands, blood vessels, and nerves in the deep dermis.

Phosphatidylcholine

It is a lipolytic substance that has been widely used under the trade name Lipostabil®. It is currently banned by both the FDA and Anvisa.

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Chapter 13
Active Agents in Injectable Drug Delivery

Bruno Messias Pires de Freitas, Karin Milleni Araujo, and Fatima Pires de Freitas

Introduction

Drug delivery is a therapeutic system which consists of carrying the active agents as close as possible to the desired location by using injectable, transdermal, loco-regional and/or sequential procedures. In order to have the best result in the area to be treated and with less adverse effect, micro-doses of specific active agents have been infused at varying depths. Drug delivery-based therapy has been adopted for tissue stimulation and revitalization through the intradermal route [2].

This treatment has been indicated for facial rejuvenation, body disharmony, stretch marks, and alopecia, among other conditions. In this chapter, the authors address the main active agents that can assist in the therapeutic approach of these conditions.

Actually, almost all drugs can be used in drug delivery-based therapy, but we should prefer water-soluble products rather than fat-soluble products. Clinicians must avoid mixing incompatible products, because it can precipitate the involved drug, forming a different product which could modify the action of the selected drug. Owing to a high allergic index, some drugs (e.g., anti-inflammatory drugs) should be avoided. Therefore, as there is a risk for cross-reactions between drugs, clinicians should be extremely cautious when preparing any mixture of products [4].

It is extremely important to work with active agents which present good local tolerability and good interaction with the tissues. Importantly, the selected active

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agent(s) should present with recognized therapeutic efficiency. We are talking about active metabolites, isotonic solutions with pH compatible with tissues, which are water-soluble and non-sensitizing [7].

The main products to be use in the conditions mentioned above are as follows.

Anesthetics

These are anesthetic drugs that can be used in blends and their actions.

Procaine

Procaine was discovered as an anesthetic in 1905, but it was used only in 1948 due to its tissue trafficking effect, that is, vasodilatory action with increasing of the capillary permeability. In mixtures, procaine is adopted as a vehicle, allowing the selected drug to persist for a longer period at the application site [5].

Procaine induces vasodilation by blocking the nerve impulse. It has also a direct action on vascular musculature – pH 3.5–4.5. It is metabolized in the liver, and its metabolites are eliminated largely by the kidneys in urine. Owing to the presence of the metabolite PABA (para-aminobenzoic acid), it is important to be careful when using the procaine. In high doses, procaine could induce seizures and pharmacologically interacts with sulfonamides [5].

Procaine is a relatively weak local anesthetic and has a short duration compared to other local anesthetic drugs, with two presentations: ampoules of 2% with 2 mL or 5 mL.

Lidocaine

Lidocaine is the most commonly used local anesthetics in all fields of dermatology. Lidocaine acts by blocking the conduction of the nerve impulse and decreasing the membrane permeability – sodium and the potassium permeability system, inhibiting the propagation pathway of the sensation of pain triggered by the stimulus [5].

It is metabolized in the liver and its metabolites are eliminated largely by the kidneys in urine.

Vasodilators

The vasodilators described below serve to improve the blood supply in the area to be treated.

Pentoxifylline

Pentoxifylline is a vasodilator that causes relaxation of vascular smooth muscle. It decreases platelet aggregation and increases the red cell flexibility. It is contraindicated for patients using anticoagulants and with a history of frequent bleeding. Pentoxifylline has two presentations: ampoules of 5 mL with 100 mg or ampoules of 2 mL with 40 mg [7].

Buflomedil 1%

Buflomedil is a vasodilator – alpha-adrenoceptor antagonist – that causes relaxation of smooth muscle cells within the vessel walls. It acts on the pre-capillary sphincter, conferring specific action on the microcirculatory unit. Dosage higher than 2 mL can cause flush and epigastric pain. It is contraindicated for patients using anticoagulants and with a history of frequent bleeding. Buflomedil has two presentations: ampoules of 5 mL with 50 mg and ampoules of 2 mL with 20 mg [7].

Melilotus and Rutin

Melilotus

Melilotus contain coumarin which acts in reducing edema and/or inflammation by increasing the venous and lymphatic flows and decreasing capillary permeability and the amount of fluid formed in the subcutaneous layer. It does not have an anticoagulant action. It stimulates the venous tone and the reabsorption of interstitial proteins originated by the increase of capillary permeability and mobility of the vessels of the lymphatic system, improving drainage [9].

Rutin

Rutin has a direct phlebotonic action, controlling the synthesis and degradation of proteoglycans. It acts in the microcirculation, with inhibition of platelet aggregation and facilitation of the erythrocyte deformity [2].

Lipolytic

Lipolytic drugs aim for reduction of the local adiposity.

Sodium Deoxycholate

Sodium deoxycholate has a detergent action, helping to disrupt the lipid bilayer of the adipocyte cell membranes. Application of sodium deoxycholate results in oncosis – destruction of adipocyte cells – by an inflammatory process that causes edema and nodule formation, increasing the permeability of adipocyte cells. This is followed by appearing of fibroblasts and increasing of fibrous septae, probably secondary to neocollagenesis [3].

This drug is preferably used in submental fat. It must be applied into the hypodermis using a spacing of about 1 cm as the halo formed by the product is 0.5 cm. Up to 10 ml can be used per therapeutic procedure. The punctures can be of 0.1 to 0.2 mL. There are some adverse effects: edema, hematoma, pain and hypoesthesia. Sodium deoxycholate has two presentations: ampoules of 2 mL with 60 mg and ampoules of 2 mL with 120 mg [3].

Antioxidants

Antioxidant agents are used for stimulating collagen and protection from oxidative stress.

Vitamin C or Ascorbic Acid

The important functions of vitamin C include the proteoglycan and collagen synthesis. It also decreases the adhesion of corneocytes, facilitating dermoepidermal hydration. Ascorbic acid has also a potent antioxidant action. Owing to the rapid

oxidation of ascorbic acid, the product must be used immediately after preparation. It can also be used to treat stretch marks. It is presented as ampoules of 2 mL with 20% buffered vitamin C. [9]

Silicon

Silicon is an element of the connective tissues that forms collagen, elastin, and proteoglycans, normalizes the cell metabolism, and inhibits the free radical formation. It also inhibits the non-enzymatic glycosylation, reducing skin aging. Moreover, silicon increases the moisturizing action on tissues by increasing the production of glucosaminoglycans. It has also an inhibitory action on peroxides, destruction of collagen, destruction of elastin, and connective fibrosis. It is presented as ampoules of 5 or 2 mL with 1 mg of silicon per each ml [9].

Alopecia

Alopecia is a condition related to body disharmony.

Minoxidil

Minoxidil is specific for hair loss, acting as a peripheral vasodilator. Minoxidil is metabolized by liver phenol sulfotransferase, resulting in a pharmacologically active molecule of hydralazine. Hydralazine produces arteriolar vasodilation, with no action on capacitance vessels. It is presented as ampoules of 0.2% with 5 mL (10 mg) and ampoules with 2 mL. Each ml has 0.5 mg of minoxidil [1].

D-Panthenol or Vitamin B5

Vitamin B5 is transformed into pantothenic acid, which is used in the formation of CoA, an essential element of the Krebs cycle. In the Krebs cycle, CoA is modified in acetyl-CoA, which is an important factor in the metabolism of carbohydrates and lipids. It is presented as ampoules with 2 mL. Each ml contains 40 mg of D-Panthenol [1].

Biotin or Vitamin H

At the organic level, it is transformed into N-carboxybiotin, interfering in the enzymatic system as a carbonization cofactor and in the transport of carboxylic radicals. It is presented as ampoules with 2 mL. Each ml contains 10 mg of Biotin [6].

Finasteride

It is a synthetic drug with antiandrogenic activity (a specific 5-alpha reductase inhibitor) which leads to a decrease in dihydrotestosterone. It is presented as ampoules with 2 mL. Each ml contains 0.05 mg [1].

Depigmenting Agents

Depigmenting agents control dyschromia.

Tranexamic Acid

Tranexamic acid is a synthetic derivative of the amino acid lysine and exerts its effect by reversibly blocking lysine binding sites on plasminogen molecules, thus inhibiting plasminogen activator from converting plasminogen to plasmin. This reduces conversion of plasminogen to plasmin (main agent responsible for fibrinolysis). The keratinocyte-generated plasminogen activator increases the activity of melanocytes. By blocking the plasminogen activator, the hyperpigmentation of melasma is hindered. It is presented as ampoules with 5 mL (50 mg/mL) or 2 mL (20 mg/mL) [8].

Deferoxamine

Deferoxamine (desferrioxamine mesilate) is one of the most widely used iron chelators. It has the ability to capture free iron; the resulting chelates (ferrioxamine complex) are rapidly excreted by the kidney. It is presented as ampoules with 500 mg in 5 mL [8].

Formula Suggestions

Some blends can be used for a myriad of conditions:

- Alopecia;
- Depigmenting agents;
- Stretch marks.

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Chapter 14
Microinfusion of Drugs into the Skin (MMP®) and Drug Delivery

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Introduction

Microinfusion of Drugs into the Skin (MMP®) is a recently described [1] technique that uses a tattoo machine for homogeneous dermal infusion of the active substance into the skin. Its precision of application in the treated area is guaranteed by the different shapes and sizes of needles available.

It is a low-cost procedure, with multiple indications and quick results.

Background

MMP® was described by Arbache et al. [1] in 2013, based on the ancient tattoo procedure, the oldest invasive route of administration. In analogy to pigment infusion into the dermis, the technique infuses drugs at the site of dermatosis.

Due to the early response in some difficult-to-manage dermatosis, such as guttate leukoderma and androgenetic alopecia, the technique quickly spread among dermatologists.

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In 2016, Contin LE [2] published a series report of two cases comparing the use of the technique with minoxidil infusion on the scalp versus MMP® alone to assess the effect of microneedling on scalp stimulation. Efficacy has been demonstrated in both cases.

The first clinical trial with preliminary results was published in JAAD in 2017, comparing the use of 5-fluorouracil with MMP® for the treatment of guttate leukoderma of the upper limbs, with microneedling with placebo (saline). Again, in both groups, there was an improvement in repigmentation for a dermatological process that was difficult to manage. This time, with superiority for the drug group.

As it is a recent technique, evidence is being collected; more clinical trials are needed for consolidation and scientific support from the dermatological community.

General Considerations

Device

The tattoo device is certified by Anvisa (Brazilian Health Surveillance Agency) for medical use; Cheyenne machine (80344980009) (Fig. 14.1; Table 14.1).

Cartridges

Cheyenne cartridges (Anvisa 80,281,110,015) are composed of multiple solid needles with 0.3-mm diameter, arranged side by side with minimal space between them. As they are solid, drugs rise by capillarity.

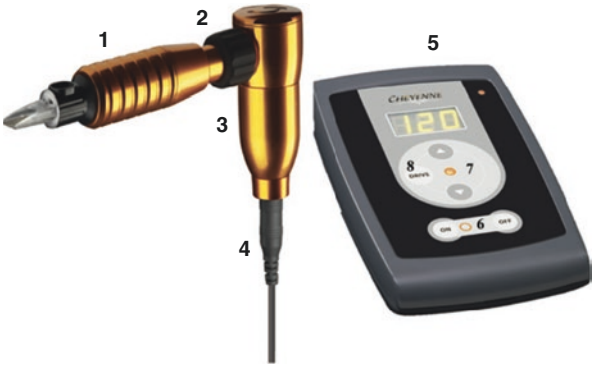

Fig. 14.1 Cheyenne machine. (*Source*: personal archive)

Table 14.1 Machine components, their functions, and features

Machine components		Features
1	Grip or hand piece	Autoclavable, standard cycle Protects the stem (most fragile part of the equipment) Rotates on its own axis, determining the length of needles
2	Screw	Autoclavable, standard cycle Fixes the grip on the engine Must be firmly coupled
3	Engine or machine	Non-autoclavable When sterilizing the grip, a protection mechanism for the stem must be ensured (an extra grip is suggested for such) It must be wrapped in sterile material to perform the procedure
4	Power cable	Connect the engine to the source
5	Source	Parameter control center
6	On and off	Through source or pedal
7	Speed adjustment	Increasing the speed increases drug diffusion, but also increases pain, bleeding, and risk of post-inflammatory hyperchromia
8	Drive	Starts needle rotation

The cartridge, after being loaded with the drug, soaks the needles that when brought back into contact with the skin, delivers the drug by an active mechanism of shear force, i.e., between cells, regardless of molecular weight and chemical constitution.

Cartridges are sold in individualized, sterilized, sealed packages, for single and individual use, and must be disposed of in an appropriate container after use. There are some variations of cartridges on the market according to the arrangement and number of needles; the choice of cartridges must be determined by the morphology of the lesion to be treated and the type of procedure to be performed (Fig. 14.2).

There are some variants of cartridges. Magnum cartridges have needles distributed in two lines parallel to each other; they are used for larger areas, e.g., face, scalp, psoriasis plaques, or dermatosis with linear conformation, such as stretch marks and surgical scars. Liner cartridges have needles distributed in the form of a rosette. They are used for punctiform dermatosis, such as guttate leukoderma, syringoma, wart, and acne scars.

The number of needles must also be chosen according to the area to be treated. Cartridges with more needles treat larger areas more quickly; however, they should be avoided in small areas, since conceptually, MMP® should be done exclusively on the lesions to be treated.

The cartridge with the largest number of needles available is Magnum, with 27 needles, but there are other presentations available, listed in Table 14.2.

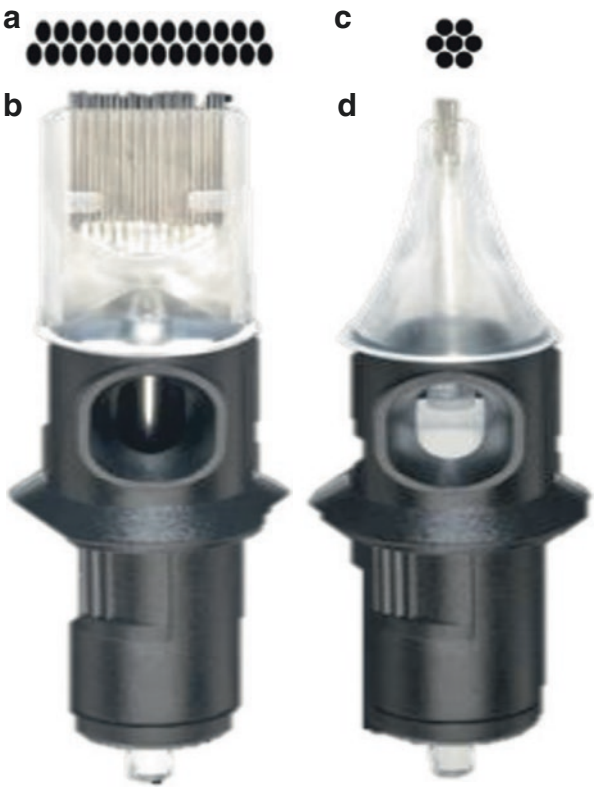

Fig. 14.2 (**a**) The Magnum cartridge 17; (**b**) Liner 7; (**c**) Magnum 27; (**d**) Liner 9. (*Source*: personal collection)

Table 14.2 Available cartridges, number of needles, and their use

Cartridge	#Needles	Use
Magnum	27	Used to accelerate treatments on large areas, such as scalp, abdomen, face, wide stretch marks
Magnum	17	Only melasma, thin and small stretch marks, eyebrows
Magnum	9	Short atrophic linear acne scars Scars Small lesions
Liner	7	Punctiform lesions Acne scars Guttate leukoderma Keloid folliculitis

Pre-Procedure

Skin Preparation

Prior skin care enhances the result and depends on the dermatosis to be treated:

- Stretch marks and melasma: The use of formulations containing tretinoin and bleaches is indicated to minimize the risk of post-inflammatory hyperchromia (PIH) [3].
- Dermatosis with thickening of the stratum corneum, e.g., viral wart and psoriasis, benefits from the previous use of keratolytics, such as salicylic acid or urea.
- Keloid and hypertrophic scars: MMP® technique is most appropriate for thin scars. In larger lesions, previous exeresis is justified to reduce keloid mass with early onset of postoperative applications.

Dermatologists should be concerned with explaining the technique in detail to patients, assessing their expectations and discipline in skin care [3].

Herpes Labialis Prophylaxis

There is no consensus, and the use of ablative procedures is at medical discretion. A systematic review by the Cochrane Skin Group in 2015 was favorable to the use of prophylaxis in patients with previous history [4]. However, in extensive facial treatments, some dermatologists use it for all patients.

Bacterial Endocarditis Prophylaxis

Based on the case report of bacterial endocarditis after tattooing [5], prophylaxis with Amoxicillin is recommended 1 hour before intervention for risk groups, i.e., congenital heart disease, previous cardiac surgery, and valvular heart disease.

Light Emitting Diode (LED)

The use of low-intensity laser reduces inflammation, stimulates healing, leads to vasodilation and analgesia; it can be performed before or immediately after the procedure. Some drugs used in MMP®, such as minoxidil, are photosensitive, which means that they can be modified by light. Therefore, in these cases, LED

must be done before the procedure [6]. Today, there are LED home devices that can be used daily for maintenance treatment of alopecia.

In facial treatments, LED is often used post-procedure to reduce inflammation, accelerate healing, and reduce pain and discomfort [7].

Informed Consent Form (ICF) and Photography

Patients should be instructed to arrive approximately 30 minutes before the procedure to sign the term and discuss possible questions regarding the procedure; also, for photographic registration.

Aseptic Technique Procedure

Drug microinfusion, aiming to respect the precepts of biosafety, is an outpatient surgical procedure, and as such, it is performed in a sterile environment. Not all components of the device are autoclavable, and they should be covered with sterile protection. The area to be treated must be cleaned repeatedly with chlorhexidine until complete removal of impurities such as topical anesthetic, makeup, and sunscreen.

Machine Assembly

Sterile assembly is easier in the presence of an assistant. The steps are explained in Table 14.3.

Source, Grip, and Engine

Outside the sterile field, the source must be supported on a rigid surface and connected to a socket by the multi-volt cable. The engine is a non-autoclavable piece that contains the stem. It must be constantly protected, as it is the most sensitive region of the device.

The assistant presents the engine with the stem toward the dressed dermatologist (Fig. 14.3), who fits the grip on the stem and turns the screw clockwise until it locks.

Table 14.3 Step by step of the MMP® procedure

	Step	Considerations
1	Sterile assembly	Sterile field: Grip, cartridge, engine protective packaging, sterile gauze, syringe, and pink needle are deposited.
2	Source	It must be placed on a rigid surface, connected to the socket through the bi-volt cable. After switching it on (ON button), the number of needle rotations is selected.
3	Grip	The assistant introduces the stem to the dermatologist, who attaches the sterile grip, turning the screw to the end.
4	Engine	Holding by the (sterile) grip, the dermatologist wraps the engine with a sterile blanket (bag, TNT, gloves) and then introduces the connector (lower region of the engine) to the assistant, who attaches the power cable.
5	Cartridge	The cartridge is attached to the anterior region of the grip. Regardless of strength, it enters and, at this point, it must be rotated clockwise. Coupling should be checked before starting rotations.
6	Drive	Exteriorization and rotation are initiated. The assistant must press the button, since the source is non-sterile. In the absence of an assistant, a pedal can be acquired and pressed to activate the drive.
7	Needle size	After exteriorization, needle size is controlled from the rotation of the grip on its own axis. Clockwise rotation externalizes, whereas counterclockwise rotation internalizes.
8	Drug aspiration	The drug must be aspirated through the syringe with pink needle and deposited in the dappen that allows the introduction of the cartridge for ascending the drug by capillarity. Care must be taken for the needles not to hit the bottom of the dappen, as they are sensitive and can lose their cut.
9	Bloody dew	Immediate dew means excessive force on the skin and absence of dew means very light pressure.

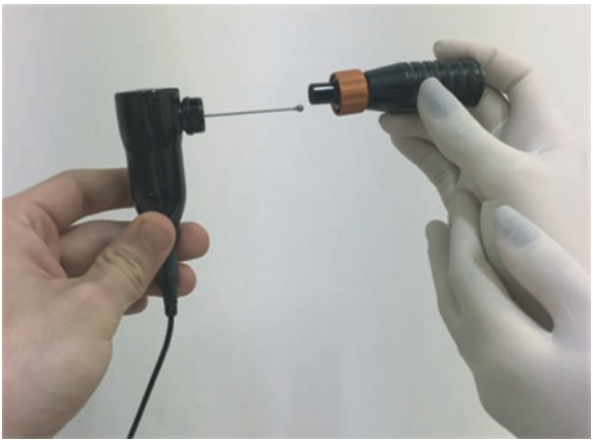

Fig. 14.3 The assistant introduces the engine to the doctor who attaches the grip to the stem. (*Source*: Personal collection)

Cartridge Coupling

The cartridge must be attached to the free tip of the grip through slight rotation until it fits and holds.

Wrapping of the Machine

Cover the non-autoclavable part of the machine with TNT or previously sterilized plastic bag (Fig. 14.4).

Turning the Machine on and Speed Adjustment

When turning on the source, the indicators in the equipment will light up. The number corresponds to needle speed in revolutions per minute (rpm). It is known that the higher the speed up to 110 revolutions per minute (60–130 are allowed by the machine), the greater the diffusion of the drug. However, risks also increase, since the higher speed triggers greater bleeding and greater risk of post-inflammatory hyperchromia, in addition to more pain.

During the learning curve of dermatologists regarding the technique, 60 revolutions per minute are advised. The speed is defined according to the protocol to be performed.

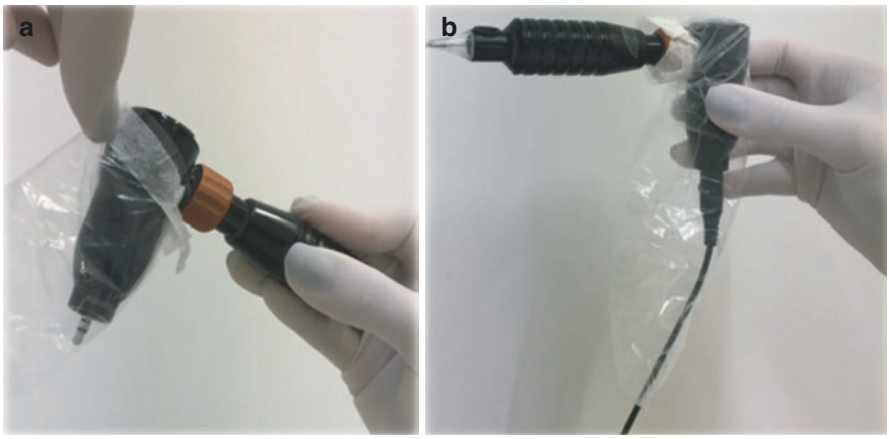

Fig. 14.4 (**a**) The doctor wraps the engine with the sterile bag. (**b**) Machine assembled sterile. (*Source*: Personal collection)

Needling Depth

The drive button generates externalization of needles, and their size is adjusted by rotating the grip on its own axis, increasing when turned clockwise and decreasing when counterclockwise.

One of the biggest questions when starting the practice of MMP® is which needling depth is best suited for each dermatosis. Much more important than that is the degree of pressure exerted by the applying doctor. For example, needles that are very externalized in those with very light hands will trigger the same degree of injury as small needles with greater pressure.

Therefore, the current guideline is to consider the bloody dew (Fig. 14.5) that each treatment deserves (see in the section Protocols) and what is the best way for you to reach it, externalizing or internalizing the needle, or controlling the level of pressure applied to the skin [8].

Anesthesia

The need for anesthetics must be analyzed on a case-by-case basis, depending on the clinical indication and the patient's tolerance threshold. Many patients consider that the burning of anesthetic penetration hurts more than the procedure, which should be discussed beforehand.

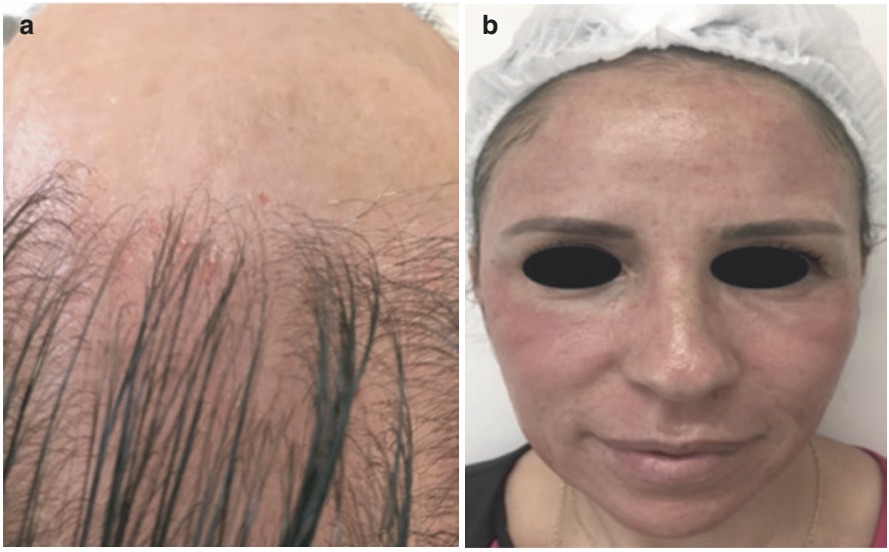

Fig. 14.5 Light bleeding dew after hair treatment (**a**) and after melasma (**b**). (*Source*: Personal collection)

Topical Anesthetics

It is recommended to use topical anesthetics in areas of more delicate skin, such as face, neck, breasts, and back of hands. Commercial drugs such as Dermomax® and EMLA® or compounding drugs can be chosen.

You should always make sure that the topical anesthetic has been completely removed before starting treatment, because it usually has high concentrations of actives that, when infused, can generate toxicity [9].

The scalp has some particularities, and the removal of creams, ointments, and gels is difficult and implies the repeated rubbing of chlorhexidine with gauze, which is usually uncomfortable and generates anxiety. If you choose topical anesthesia, spray is recommended.

Body treatments often do not require or contraindicate the use of topical anesthetics, as the size of the treated area is extensive, requiring very high amounts of topical substances, which can cause intoxication, e.g., stretch marks and guttate leukoderma.

Neural Block

In dermatosis that requires application with more pressure, such as acne scars, or in delicate areas such as the periocular or perilabial area, neural block can be chosen, made with 1–2 ml per nerve of lidocaine (1% or 2%) or bupivacaine (0.25% or 0.5%) without adrenaline.

An option for the scalp is regional block above the eyebrows (Fig. 14.8) or ring block, bordering the frontal implantation line (or where it should be). In this case, 4 points of 0.5 ml are applied, trying to reach and soak the branches that ascend from the supraorbital foramen [10].

After blocking, wait between 15 and 30 minutes to start treatment.

Infiltrative Anesthesia

In infiltrative anesthesia, depending on the size of the treated area, Klein's tumescent formula can be use, which has been described as 1000 ml of saline, 50 to 100 ml of 1% lidocaine, 1 ml of epinephrine 1:1000 and 12.5 ml of sodium bicarbonate; dilution can be made proportionally with smaller volumes.

It should be considered in combinations of techniques, e.g., subcision in acne scars or stretch marks, or in more aggressive treatments of the eyelids.

Other Mechanisms of Analgesia

One way to change pain sensitivity is using ice compresses immediately before application, but it is known that ice decreases the speed of drug diffusion and its influence on MMP® is unknown.

Another alternative is skin compression with the fingers of the other hand, making a skin fold. This technique has been described for use on the scalp with the justification that removal of the skin from the richly innervated periosteum reduces pain sensation, but there are satisfactory results in body treatments, as there is also a change in pain perception [11].

Drug Aspiration

With the drive turned on and needles externalized, the dermatologist takes them to the drug deposited in the dappen.

Procedure Description

After aspirating the drug, microinfusion starts perpendicularly to the skin. The 90° angle is the one that allows greater penetration with less epidermal damage.

The needles must not be dragged, but applied gently in continuous and repetitive point movements. Dragging the needles can generate iatrogenesis, e.g., fracture of the hair shaft in scalp treatments or scratching of the skin in facial and body treatments.

Guttate leukoderma is an exception to this rule; lesions must be completely filled in snail with the Liner needle, covering the entire area of acromia (Fig. 14.6).

Periodically, cartridges must be refilled with drugs. The entire area must be treated.

Bloody Dew

Bloody dew is a sign that the drug has been dermally delivered, since the epidermis is nonvascular [12]. Due to the small diameter of needles (0.3 mm), dew is not immediate after piercing the skin, taking approximately 20 seconds. To obtain the recommended level of pressure to be exerted in each dermatosis, the doctor must

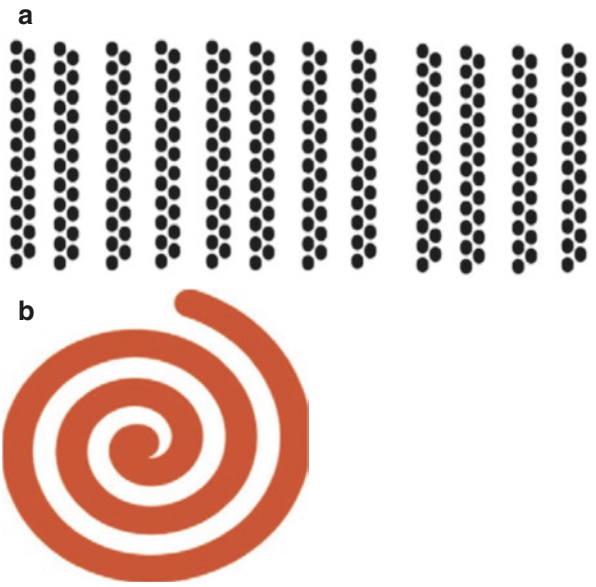

Fig. 14.6 Needle application methods. (**a**) Punctuated and repetitive. (**b**) Snail. (*Source*: Personal collection)

practice on artificial skin. As applying dermatologists become more experienced, they get to knows better the level of pressure they should exert for each area and for each patient.

In bilateral treatments, the other side should be reviewed after the end of treatment. For example, stretch marks on the buttocks: one side is treated, and then the other and, finally, the doctor should return to the previous one to see if any area has been left untreated. The same goes for guttate leukoderma; often it is a partial lesion or just some lesions in a limb full of them, so it is worth going back to assess the other limb after treatment.

Drugs

The drug used must be sterile and packaged in an ampoule or vial that ensures biosafety. Ampoules must be fully used in an application and any residue must be disregarded. Vials can be used in more than one application, as long as they are always aspirated by sterile needles and stored in an appropriate place according to the manufacturer.

The drug should be aspirated with disposable syringes and needles, and placed in a wide mouth sterile container that allows the introduction of the MMP® cartridge. A container that meets the specifications is the dappen used by dentists: it is a small, autoclavable glass container.

Some dermatoses are treated with just one drug, others with a mixture of drugs. Since the pharmacokinetics of drugs administered via MMP® is unknown, caution is recommended as for oral drugs, i.e., the same contraindications, laboratory follow-up, and restrictions.

0.5% Minoxidil

It has vasodilating and antiandrogenic effects. It acts on hair growth by increasing blood flow to the skin. It causes synchronization of capillary cycle that normally occurs in mosaic, which can generate an initial effluvium. It should be avoided in patients who already have effluvium, as it can worsen it. Its molecule is photosensitive; therefore, it is supplied in a light-protected ampoule that must be opened immediately before use and should not be administered before exposure to LED [13].

0.05% Finasteride

The drug is oily, but stable and can be used in combination with minoxidil (a mixture widely used for androgenetic alopecia). It is an antiandrogenic hormone that inhibits 5-alpha reductase, a testosterone-converting enzyme in its most potent form, dihydrotestosterone. It is used for prostatic hyperplasia, hirsutism, and baldness. It is contraindicated in women of childbearing potential without the use of contraception and lactating women due to the risk of feminization of male fetus [14].

Patients who experienced side effects or an allergic reaction to the oral drug should be considered contraindicated for use via MMP®. A case of impotence after application of finasteride via MMP® was reported in a patient who had complained of decreased libido with oral use.

22.2% Vitamin C

This is widely used by dermatologists as an antioxidant for rejuvenation treatment and for white stretch marks [15]. However, experience with vitamin C applied with MMP® is higher prevalence of post-inflammatory hyperchromia when compared to the application of other drugs. Therefore, it should be used with caution in selected cases.

In addition, it is a photosensitive drug that oxidizes when exposed to light, so the same recommendations for use as minoxidil should be followed.

5-Fluorouracil (5FU)

It is a chemotherapy drug that inhibits cell proliferation. It is an irritating substance, highly toxic. Because it is a salt, it leaves a halo around the treated area.

It is contraindicated in patients with hepatic, renal, or bone marrow disorders. It is also contraindicated in cases of changes in nutritional status and blood problems, pregnancy and lactation, infections and patients undergoing major surgical procedures. Laboratory follow-up: blood count, and liver and kidney function before each session.

Treatment should be stopped if leukocytes <3500 and platelets <100,000, stomatitis, esophagitis, constant vomiting, persistent diarrhea, ulcer, or gastrointestinal bleeding. Treatment should be suspended in cases of infection. Prolonged suppression of the immune system can stimulate the development of other tumors.

It can be stored, as the bottle is usually not used all at once. It should be kept at room temperature, 15 °C and 30 °C, protected from light. Low temperatures can generate precipitates; in this case, it is advisable to carefully heat the ampoules to 60 °C, and then stir them.

Bleomycin

Chemotherapy that is a cytotoxic antibiotic isolated from cultures of *Streptomyces verticillus*. It was initially described in punctures for treatment of viral warts by Shelley and Shelley in 1991 [16]. It has shown renal elimination, pulmonary toxicity in 10% of patients; it is teratogenic and irritating to the skin. Gloves should always be used for handling. It should be stored in a refrigerator.

Its application usually generates hyperchromia and patients must be advised in this regard.

Tranexamic Acid

A drug that competently inhibits the plasmin used to control and prevent bleeding. It should be used with caution in patients at risk for thrombosis, and is contraindicated in pregnancy and lactation. Alternative to melasma due to plasmin, it is present among basal cells, being an inducer of the release of fibroblast growth factor (bFGF), stimulating the growth of melanocytes [17]. Storage: protected from light, between 15 °C and 30 °C, and humidity.

Methotrexate

With the exception of prednisone, methotrexate is the oral immunosuppressant most prescribed by dermatologists [18]. It is an analog of folic acid, and its mechanism of action is dihydrofolate reductase inhibition. It goes through hepatic metabolism and renal elimination. Absolute contraindications are pregnancy, lactation and hematological alterations, and relative ones are change in renal function, alcoholism, diabetes and obesity, liver disease or hepatotoxic drugs, active or latent infectious diseases, immunodeficiencies, and age over 65 years.

It must be kept at room temperature (below 25 °C), protected from light.

Corticoids

The immunosuppressant most used by dermatologists. It should be noted that local injections reduce, but do not eliminate systemic effects.

The dilution in saline is the same as the one used for mesotherapy: 1:1, 1:2, or 1:4, depending on the nature, location, and size of the lesion.

Storage at room temperature from 15 °C to 30 °C, protected from light. Do not freeze.

Contraindications: Infectious processes, pregnancy, and lactation.

Commercial Drugs

Many commercial drugs have been developed for drug delivery, even today there are segments of the industry focused exclusively on sterile drugs. Outside the country, this segment is much more advanced. Drugs produced for use in drug delivery can be used for MMP®.

Protocols

MMP® is indicated for use in superficial and deep dermatoses, due to the diffusion halo in the skin.

Alopecia

Trichology-guided anamnesis and laboratory tests should be the same as dermatologists would indicate for patients on systemic drugs.

Patients should be advised that MMP® is a complementary technique in capillary diseases and that it will not replace any treatment established in the literature. Patients must sign the ICF and understand that it is a relatively new technique and that, therefore, there are unknown adverse events for long-term follow-up. It has been intensively studied, and it should be offered responsibly with caution to patients.

Photographs are taken in pre-established positions so that they can be compared later. The use of trichoscopy records to show improvement is important for follow-up sensitivity, demonstrating the clinical response or the absence of it earlier (Fig. 14.7).

In case of infection at the application site, such as pustules and seborrheic dermatitis, the clinical treatment of such should precede the application.

After LED, the patient should be positioned comfortably in the supine position. The sitting position should be avoided, as there are cases of syncope due to vagal reflex. The use of cushions below the occipital region is recommended, raising the apex to allow access to the entire upper area of the scalp (Fig. 14.8). Dermatosis located in the occipital region can be treated with patients in the prone position.

It is important to follow an application order to avoid untreated areas; for such, each doctor must define their conduct. You can start on one side, separate with the comb handle the other side, applying to the lines, respecting the direction of rods. Another way is to divide the scalp into quadrants, separating them with clips and performing the treatment in each quadrant at a time. In patients with severe baldness, it is possible to draw quadrants with a white marking pencil.

Application across the stem may result in fracture. Therefore, in swirls, application must respect the anatomy of follicles. The needle must be at 90° and must not

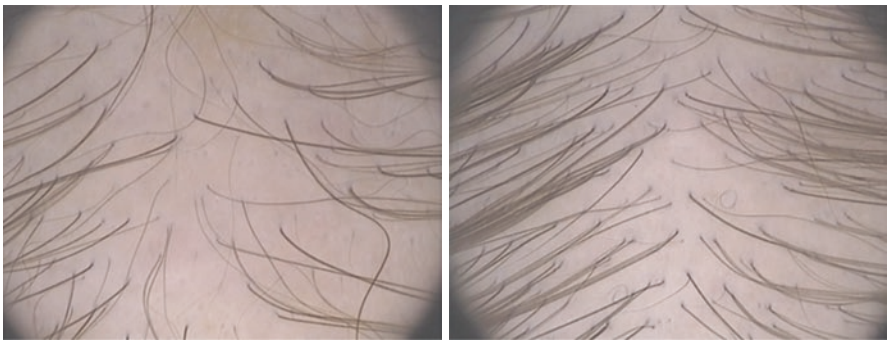

Fig. 14.7 Result after four sessions of MMP® with minoxidil and finasteride for androgenetic alopecia. (Courtesy Dra Dirlene Roth)

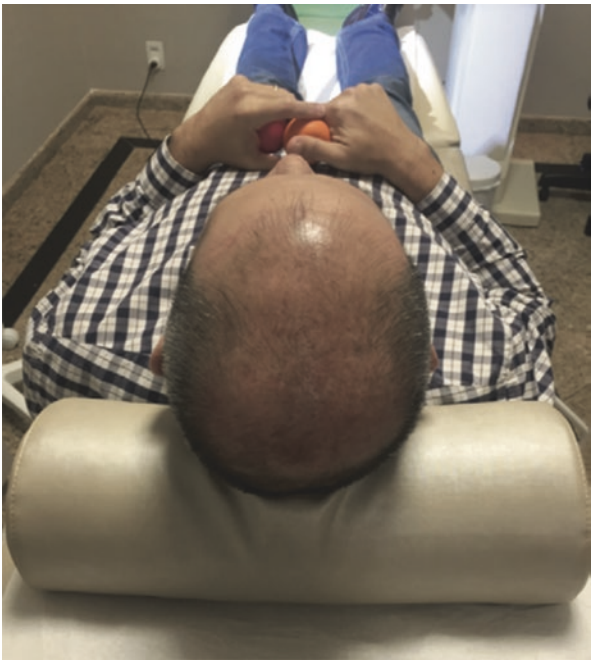

Fig. 14.8 Patient in prone position with pad under the posterior cervical region that allows access to the entire upper region of the scalp. (*Source*: Personal collection)

be dragged to avoid hair tonsure. On the scalp, a speed of 60 rpm should be maintained.

Androgenetic Alopecia

Drug microinfusion into the skin presents its most promising results and is widespread among dermatologists who use the technique in androgenetic alopecia [2]. However, it should not be indicated to patients as a heroic measure, since the results are heterogeneous, with individual variability, and, as previously stated, complementary.

The Magnum 27 needle decreases treatment time, as it increases the area of contact with the skin. Drugs used are finasteride and minoxidil. It must be associated with home treatment.

The treatment respects the hair cycle: Once a month for 3 months, then a maintenance phase with an interval of 3 months, 6 months, and annually (Figs. 14.9 and 14.10).

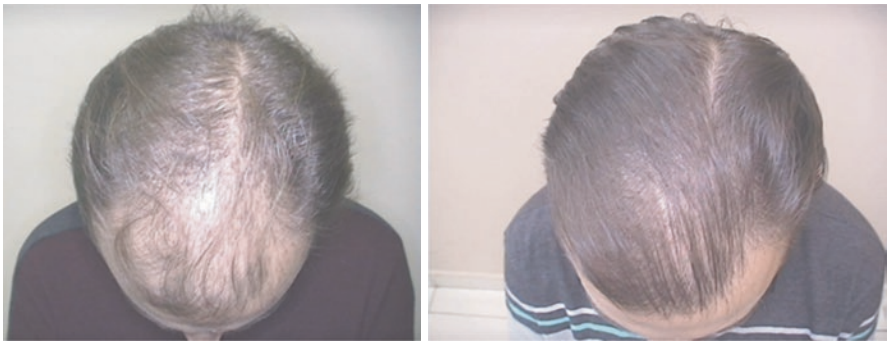

Fig. 14.9 Result after four sessions of MMP® with minoxidil and finasteride for androgenetic alopecia, photographed in the eighth month. (Courtesy Dra Dirlene Roth)

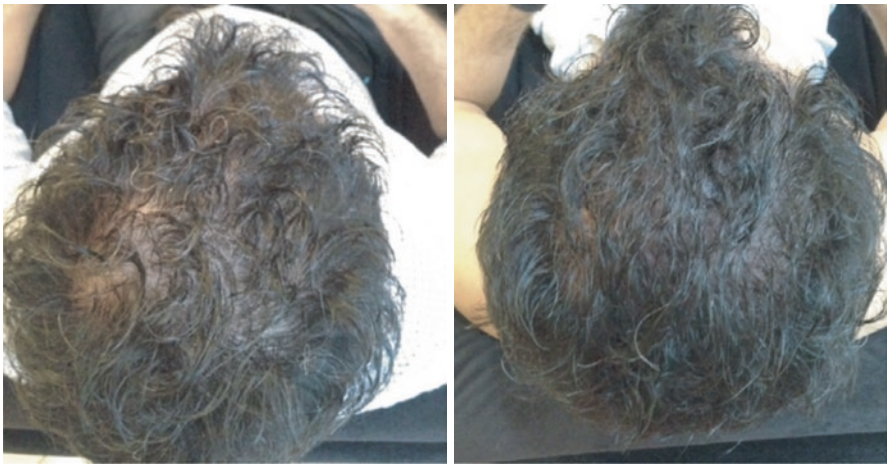

Fig. 14.10 Result after one session of MMP® with minoxidil and finasteride for androgenetic alopecia. (*Source*: Personal archive)

Alopecia Areata

Treatment with MMP® replaces the conventional application of corticosteroids in intralesional infiltration, reducing the occurrence of atrophy resulting from drug accumulation (Fig. 14.11).

In alopecia areata, monthly applications are recommended until there is reduction in disease activity, which is assessed by pull test and dermatoscopy (presence of black dots and peladic hair). Home treatment should not be interrupted.

Cartridge size will depend on disease dimension and the size of plaques. The level of dew will depend on the sick location. Diseases located in the beard and eyebrows should be handled with less pressure than the scalp.

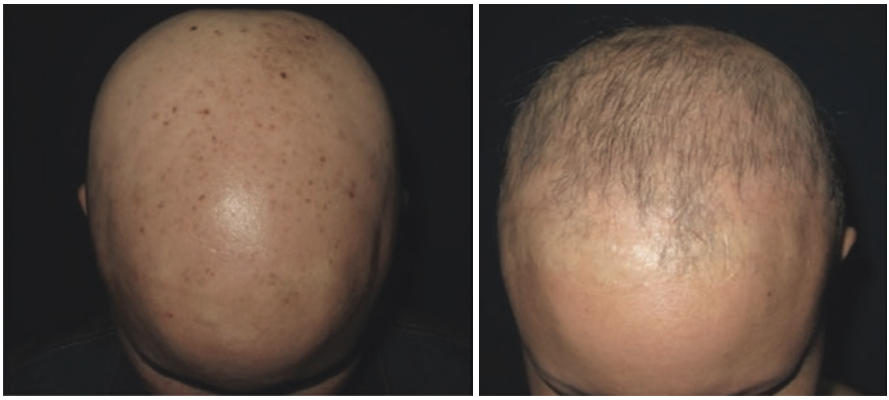

Fig. 14.11 Alopecia areata universal treated with MMP® with corticosteroids. (*Source*: Personal collection)

Frontal Fibrosing Alopecia/Lichen Planopilaris

As in alopecia areata, intralesional infusion is performed with the same conventional protocols. These are complex diseases that must be managed by dermatologists with greater experience in trichology and MMP®.

Effluvium

Effluvium treatment, as it is self-limiting, is controversial and can even lead to heightening and worsening of the condition. The use of minoxidil is contraindicated because it has the ability to trigger effluvium.

Stem Fragility

A very common complaint among women who visit the trichologist's office is stem fragility that occurs due to the excess of chemicals and tinctures. Drug microinfusion has the benefit of stem nutrition in these cases. Vitamins, amino acids, and growth factors can be used.

Pre-malignancy and Skin Cancer

There is no evidence whatsoever for the use of MMP® in pre-malignant and malignant lesions. Before proposing to treat cancer fields with whatever technique, dermatologists must be trained to diagnose malignancies or pre-malignancies from dermatoscopy, and suspected areas must be biopsied. There are descriptions of the use of intralesional infiltrations with 5-fluorouracil, bleomycin, and methotrexate with good response for actinic keratosis, basal cell carcinoma, and squamous cell carcinoma in situ, in addition to works with fractional laser associated with Effurix. The drug used in MMP® is pure 5-fluorouracil, without dilution (Fig. 14.12).

The cartridge must be Magnum and the number of needles will depend on the size of the treated area. It must be applied in snail, from outside to the inside of the lesion, avoiding cell inoculation in healthy skin. Initially treat the field, leaving lesions for last.

The evaluation regarding the need for complementary application must be performed monthly through dermatoscopy and biopsies. This treatment should be discouraged for dermatologists with no experience in handling skin tumors, since there is a risk, at least theoretical, of releasing and inoculating tumor cells. It can be used in superficial basal cell carcinoma and Bowen's disease in low-risk places and minor injuries.

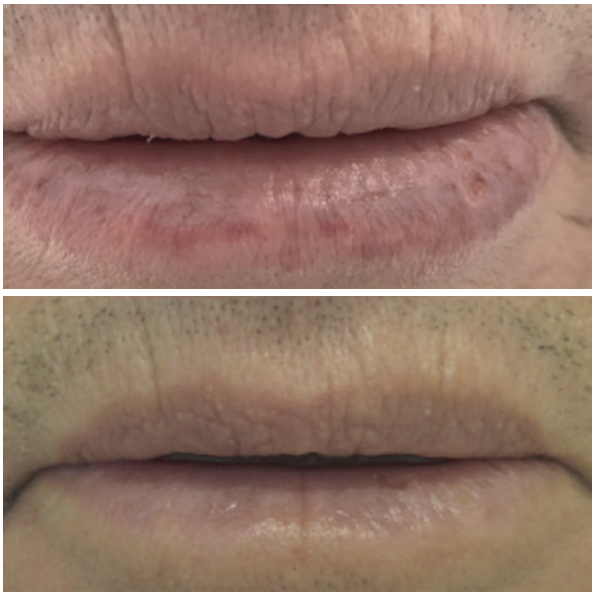

Fig. 14.12 Actinic cheilitis. Upper and lower lip treated with two sessions of MMP® with 5FU with monthly interval. (*Source*: Personal collection)

Scars

It is a promising treatment. Cartridges selected depend on the conformation of the case under treatment. In these cases, the pressure level should be more intense, as the aim is to break fibrosis. Monthly sessions are held until the aesthetically objectified result is achieved.

Acne Scars

Ice picks and distensible scars have a satisfactory response to treatment with MMP® with 5FU. Liner cartridge 7 or 9 can be used and the drug must be applied in back and forth movements with moderate-intense pressure. Topical anesthesia is usually enough; lesion compression with the index finger and thumb of the other hand gives more firmness, as regions such as the malar one, without bone support, need; it also helps to mask the pain.

Some cases of multiple scars have a flaccid aspect on the face. The best results are obtained when drugs to stimulate neocolagenesis in the rest of the face are associated with scar treatment.

The number of sessions depends on the degree of scarring. An alternative that accelerates improvement is the association of the subcision technique (Fig. 14.13); however, due to bruising, there is a greater need to avoid activities. Usually in the

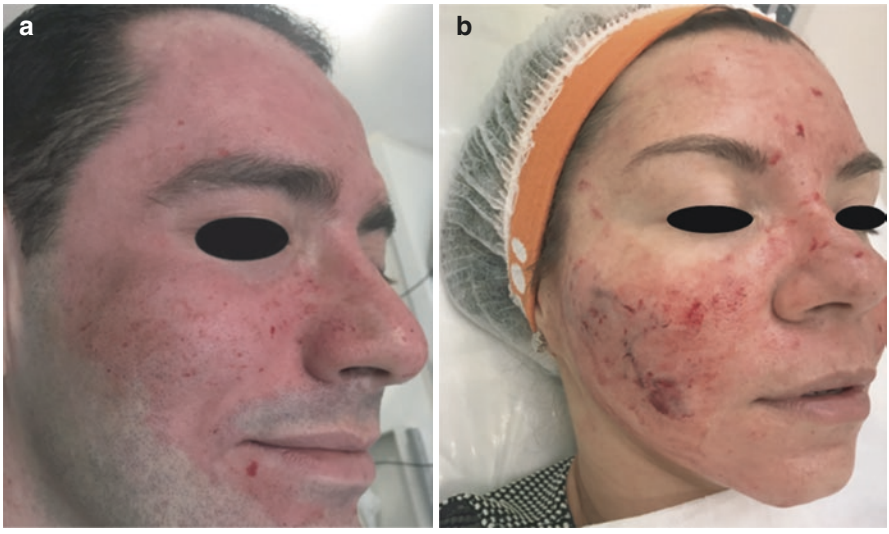

Fig. 14.13 MMP® immediate powder for acne scars in a patient with melasma. 5FU with needle liner on acne scars and full face tranexamic acid. (**a**) Ice pick scars. (**b**) Association of subcision + MMP® techniques. (*Source*: Personal collection)

treatment of acne scars with MMP®, patients are already able to work the next day with SPF, color and makeup (Fig. 14.14).

Hypertrophic Scar/Keloid

Not very advanced cases should be handled initially with 5FU [19]. Refractory or thick cases are treated with bleomycin associated with triamcinolone acetonide.

It is recommended that bleomycin be used only after intimacy with the technique.

Monthly sessions are held until a satisfactory aesthetic result is obtained. The number of sessions depends on the volume of the tumor mass (Fig. 14.15).

Linear/Achromic Scar with Fibrosis

Perhaps this is one of the most innovative responses of the technique. It is recommended to apply 5-fluorouracil as soon as possible after the surgical procedure. Three sessions are indicated at monthly intervals, but depending on the degree of fibrosis, more or less sessions may be required (Figs. 14.16 and 14.17).

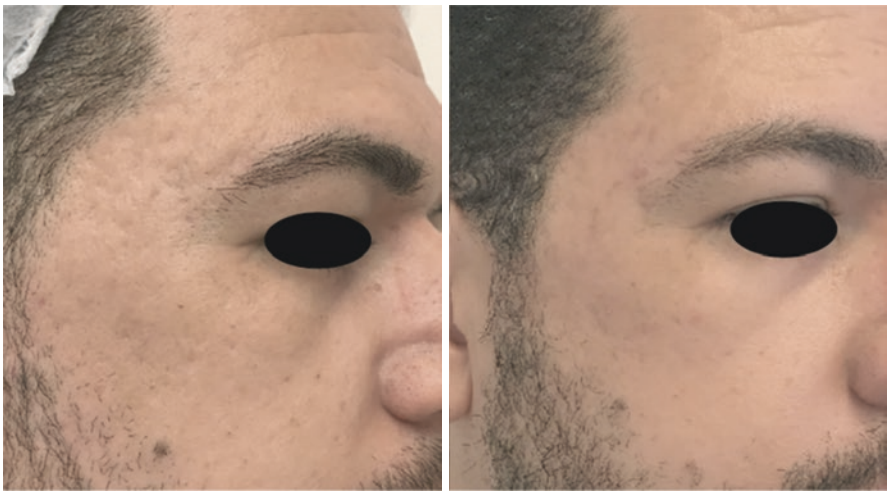

Fig. 14.14 Acne scars: the scars were treated with 5FU applied with a liner needle, then the entire face was treated with antiaging with a magnum needle. I photographed it after 1 month of the first session. (*Source*: Personal collection)

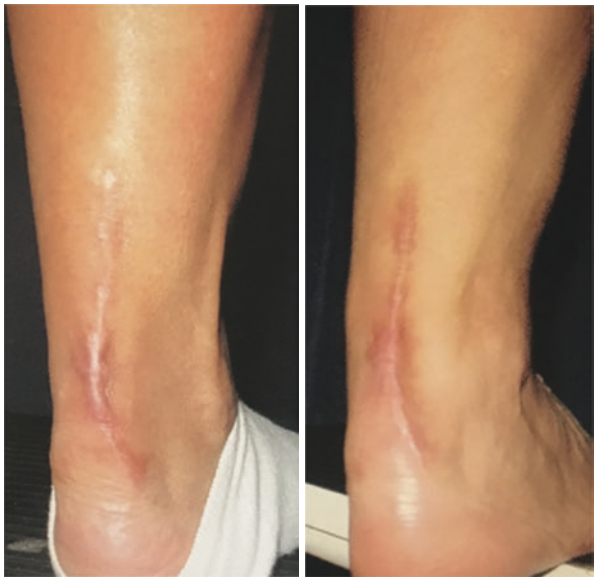

Fig. 14.15 Hypertrophic scar treated with one session of MMP® with 5FU. (*Source*: Personal collection)

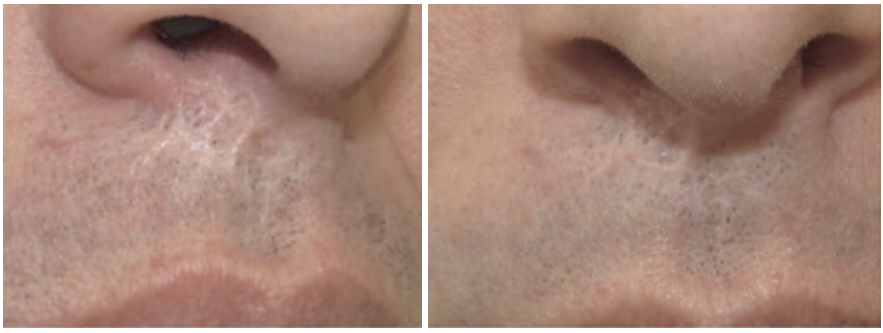

Fig. 14.16 Linear scar treated with one session of MMP® with 5FU. (*Source*: Personal collection)

Stretch Marks

The technique has shown satisfactory results in the treatment of both red and white streaks. At the moment, it is indicated to treat stretch marks with specific blends that can be purchased in drugstores or compounding pharmacies.

There is intense edema within 8 minutes with spontaneous remission after 1 hour (Fig. 14.18).

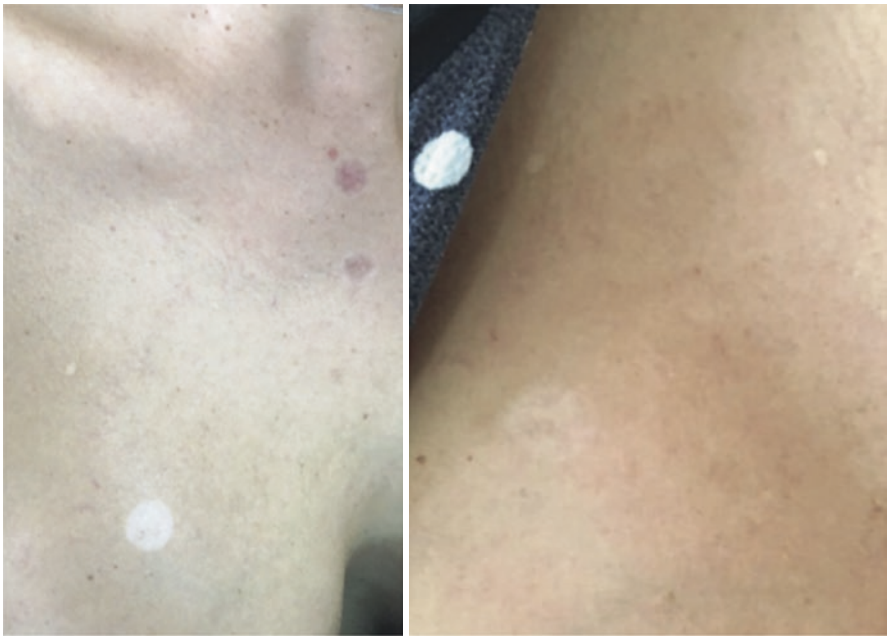

Fig. 14.17 Achromic scar after burning with intense pulsed light treated with one session of MMP® with 5FU. (Courtesy: Dr. Ritha de Cássia Capelato Rocha)

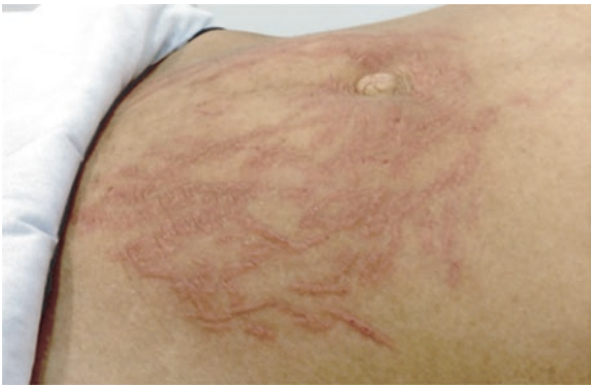

Fig. 14.18 Edema in the immediate post application of MMP® in abdominal stretch marks. (*Source*: Personal archive)

The precision of the technique allows the treatment of high phototypes with good results and without post-inflammatory hyperchromia. The vast majority of patients develop some degree of transient hyperchromia for approximately 15 to 20 days. There is spontaneous remission, or use of bleaches or peelings.

The combination of techniques can be favorable in the case of flaccidity, e.g., postpartum; roller can be applied to the entire area and MMP® specifically to stretch marks (Fig. 14.19).

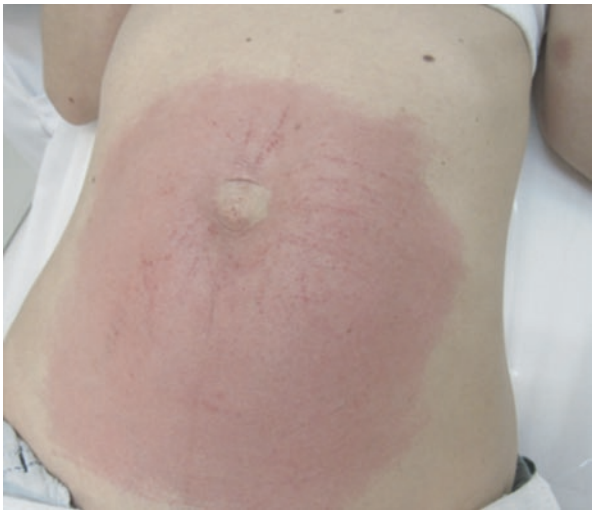

Fig. 14.19 Association of microneedling with roller and MMP® in stretch marks and postpartum abdominal flaccidity. (*Source*: Personal archive)

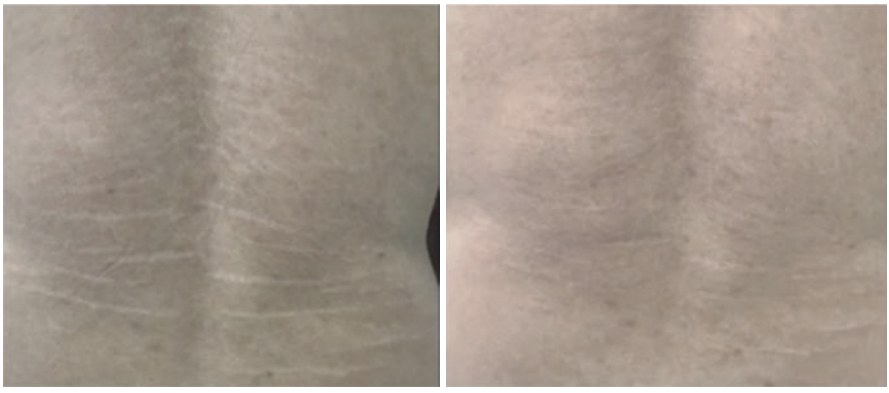

Fig. 14.20 Alba striae treated with one session of MMP® with manipulated glycosaminoglycans. (*Source*: Courtesy of Dr. Ana Paula Coelho)

In these cases, the percentage of post-inflammatory hyperchromia is usually higher. In high phototypes, the roller can be replaced by MMP® at the edges of the lesion, covering a slightly larger area than in the stretch marks. It is recommended that this type of treatment is started only after the first session, so that the doctor knows the response of that type of skin in case of hyperchromia; it is worth using bleaches for longer before any bolder maneuver. The benefit of concomitant use of hydrolyzed collagen with treatment for stretch marks and body flaccidity is described.

Generally, 3 monthly sessions are indicated, but the need may vary depending on the degree of rupture of the skin and the degree of distension of that stretch mark (Fig. 14.20).

Red stretch marks can be associated with intense pulsed light, with an interval of 1 month between applications. Stretch marks due to cushing after therapy with corticoids do not usually respond well. In cases of rheumatological diseases, a counter-referral letter is suggested to rheumatologists explaining the procedure and requesting clearance.

It is not recommended to apply to more than one body area at a time.

The use of topical anesthetics should be discussed with patients, since the area of anesthesia can overcome the toxic dose. Often, the applying physician is able to mask the pain by clamping the area between the thumb and index finger of the other hand, which also helps to firm the skin; especially in cases of flaccidity, it greatly facilitates the application.

Guttate Leukoderma

Already published in JAAD, it presents a fast and overwhelming response to an application session with 5FU on Liner tip. Two sessions are recommended, with an interval of 4 weeks, for review and complementation, if necessary. As sun damage is chronic, new lesions may appear. Some rare patients had recurrence (Fig. 14.21).

Melasma

Every melasma must be viewed with care. A very light hand is oriented; there is almost no bloody dew, plus diffuse erythema. Some areas such as eyelids and nose tend to dew even with a very light hand.

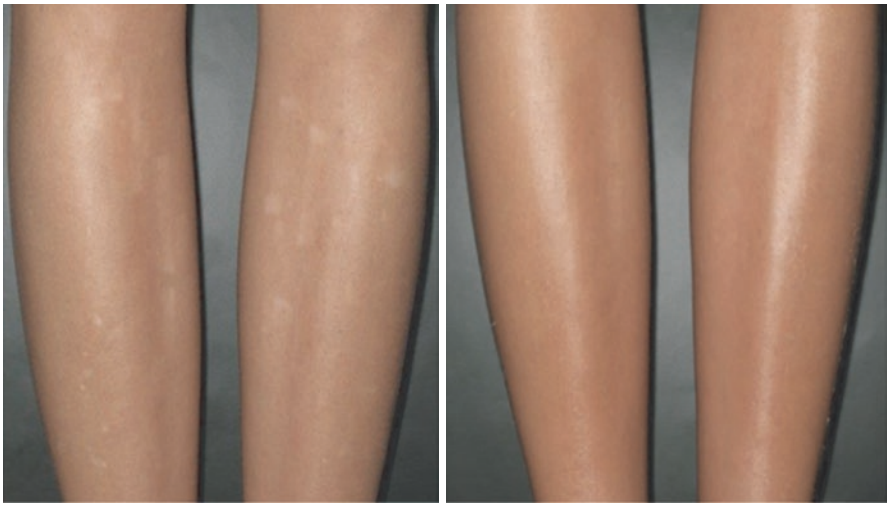

Fig. 14.21 Guttate leukoderma and aching scars on the lower limbs treated with one session of MMP® with 5FU. (*Source*: Personal collection)

During the learning curve, it is advised that dermatologists do not drag the machine over the patient's skin, as there have been many cases of scratches with this technique.

The face should always be anesthetized in facial treatments. Topical anesthesia is usually sufficient in melasma treatments, as the application is very light, but some patients with greater sensitivity and areas such as the eyelid and perioral may require blockage.

There is a phenomenon described for melasma and some ablative procedures in melasma that occur approximately 1 or 2 weeks after application, which is a transient darkening explained by the extrusion of melanin through the microcolumns created by the needle inlet. This usually occurs in most cases (Fig. 14.22).

The protocol consists of 3 monthly applications (Fig. 14.23), which can increase according to the needs of each patient. It is recommended that, after 15 days of application, patients undergo diamond or retinoic peeling to minimize the darkening phenomenon.

Home treatment should be maintained throughout the protocol, except in post-immediate cases, if there is sensitivity.

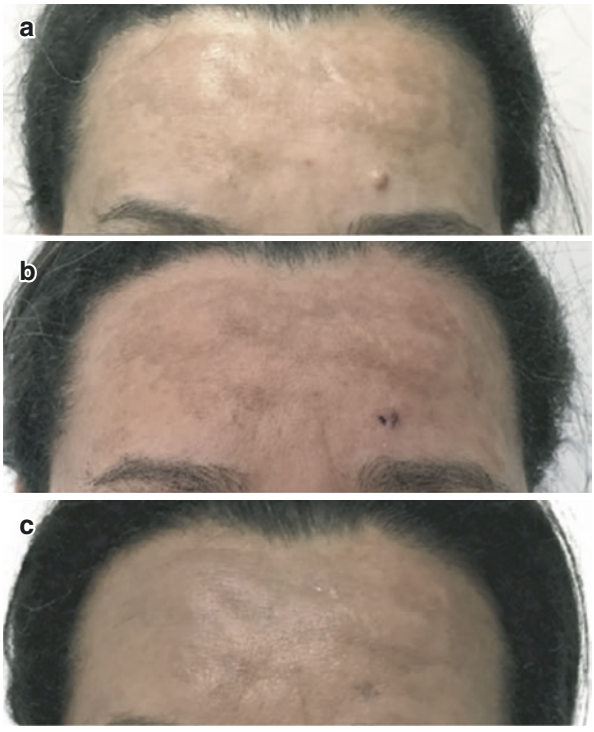

Fig. 14.22 Melasma treated with one session of MMP® with tranexamic acid. (**a**) Pre-treatment. (**b**) Transient worsening after 15 days. (**c**) After 1 month

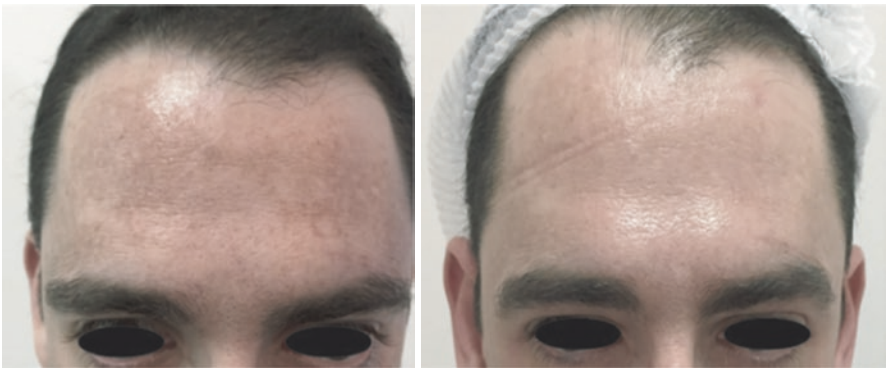

Fig. 14.23 Melasma treated with one session of MMP® with tranexamic acid. (*Source*: Personal archive)

Rejuvenation

With the assumption of ablative technique, one can understand the benefit of the technique on rejuvenation [20]. Various commercial or non-commercial drugs are already sold for this purpose. Magnum 27 should be used for greater coverage and shorter application time.

The hand should be light for treatment with melasma. In the deepest wrinkles, a second pass should be made, like staking on an ablative laser.

The face, neck, and back and front of the hands can be treated in the same session, always taking into account the size of the treated area and the risk of toxicity of topical anesthetics.

The most used drugs are vitamin C, hyaluronic acid, and commercial drugs. The protocol is three sessions with monthly interval (Figs. 14.24 and 14.25).

Syringoma

The use of MMP® for syringomas resolves definitively and with minimal epidermal damage. There is no long follow-up of patients, as the technique has recently been described.

Bleomycin is used with Liner needles with intense pressure until the rupture of the lesion capsule is felt.

Complete remission of lesions usually takes approximately 2 months, but when treated satisfactorily (the needle must be squeezed until the capsule is broken), they disappear in one session (Fig. 14.26).

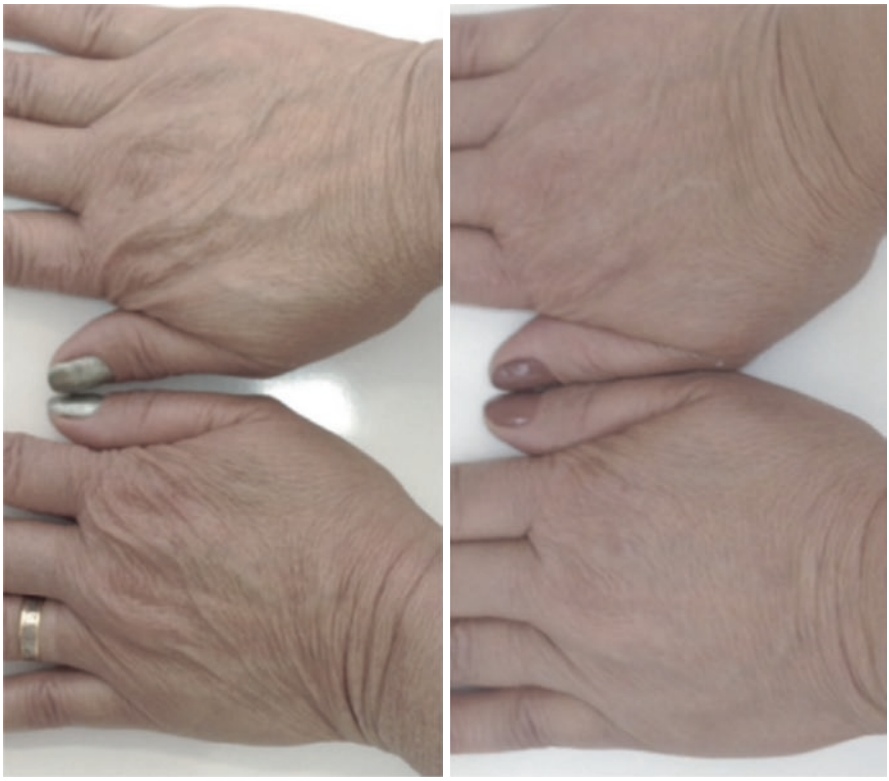

Fig. 14.24 Treatment of the back of the hands with 1 session of MMP® with hyaluronic acid. (*Source*: Personal collection)

Psoriasis

Safety and efficacy protocols for the treatment of psoriasis with MMP® are still being studied and should be considered as alternative therapy. In cases where conventional therapy has failed or side effects have occurred, or in places of difficult treatment, such as nail lesions, MMP® offers good tolerability for corticosteroid application (Fig. 14.27).

As stated earlier, caution with systemic drugs must be taken for use with MMP® until works on pharmacodynamics are published. Therefore, it is necessary to collect previous and control tests according to the risks associated with the chosen drug.

The drugs used are immunosuppressive: Methotrexate and ciclosporin. Methotrexate is applied pure and cyclosporine is diluted in three parts of saline to decrease its viscosity.

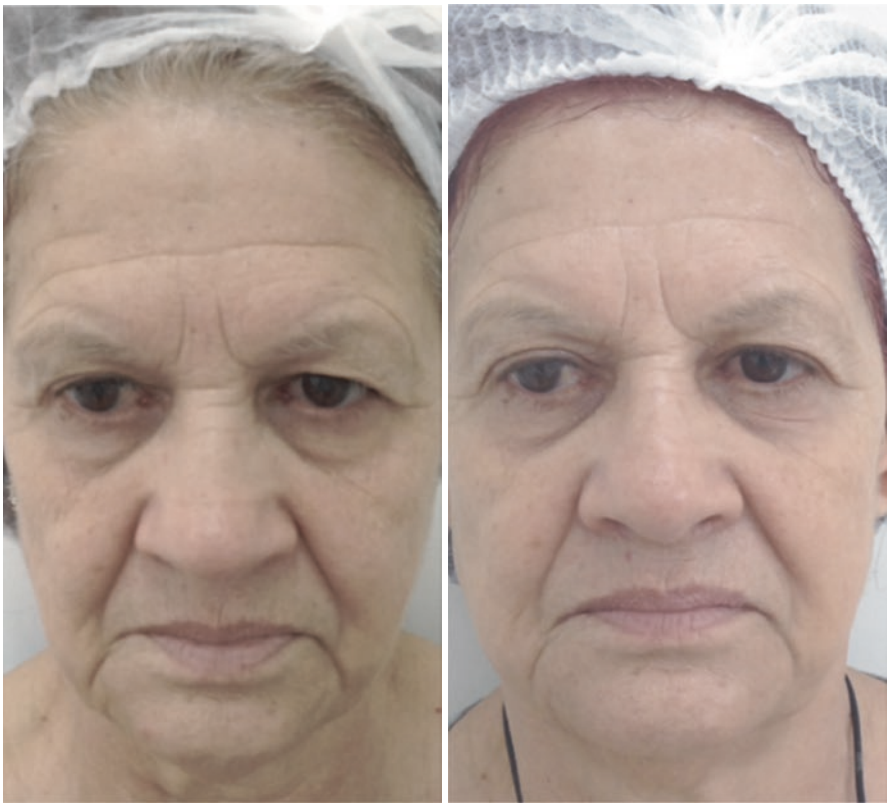

Fig. 14.25 Treatment of the back of the hands with one session of MMP®. (*Source*: Personal collection)

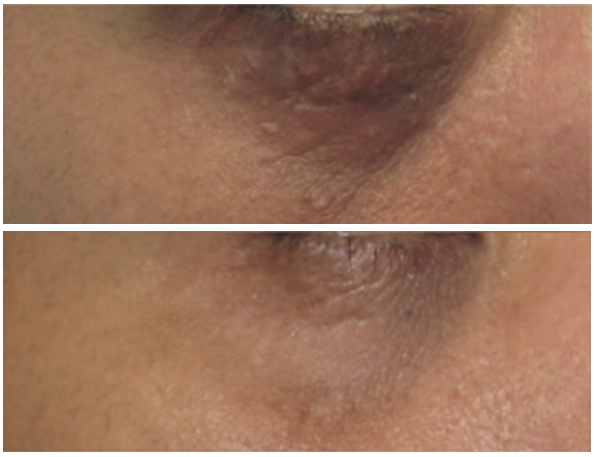

Fig. 14.26 Syringoma treatment with one session of MMP® with 5FU. (*Source*: Personal archive)

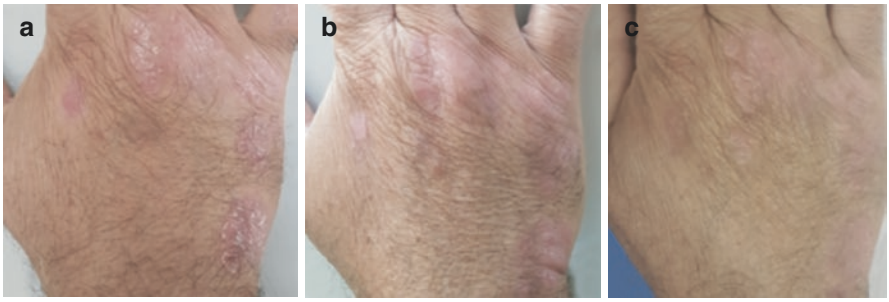

Fig. 14.27 Psoriasis treated with MMP® with cyclosporine. (**a**) Pre-treatment. (**b**) After the first session. (**c**) After the third session. (Courtesy Dra Aline Okita)

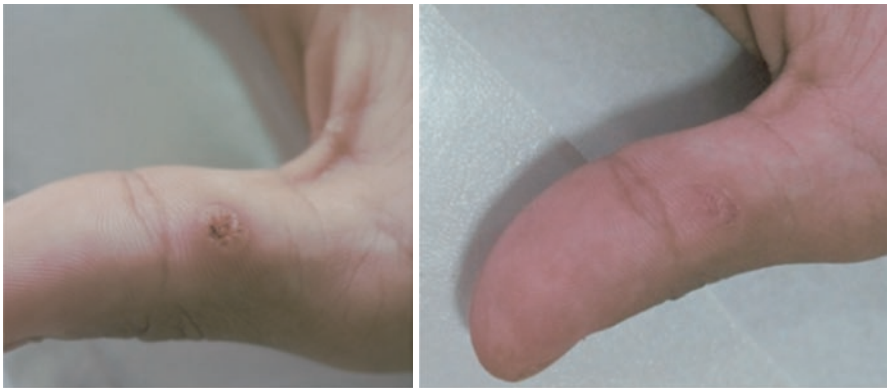

Fig. 14.28 Common wart treated with one session of MMP® with bleomycin. (Courtesy Dr. Maria Teresa Soares)

Vitiligo

The casuistry is still small, with a very variable response, and it should be applied only to lesions so that there is no risk of Koebner's phenomenon. Diluted triamcinolone 2.5 mg/ml is applied.

Warts

The application should be made with greater pressure on viral warts, and the drug used is bleomycin, with good results (Fig. 14.28).

Post-Procedure

Patients should be instructed not to wash the treated area for 6 to 12 hours (look for the article on how long holes are open after microneedling), and should avoid using sunscreen or other topical substances on the day of the procedure.

The next day, soothing cream is recommended. Flaking of the treated area may occur. There should be guidance regarding this, including for hair treatments, as it often generates concern on the part of the patient.

Contraindications

Same contraindications for oral drugs, microneedling with roller and ablative laser. Presence of systemic infection or at the treatment site, decompensated systemic disease; in compensated cases, discussion with the patient's physician is recommended. Gestation or lactation.

Complications

- Post-inflammatory hyperchromia (Fig. 14.29): High phototypes are not considered contraindications, but should be handled more carefully. They are usually transient and treated with bleachers and sun photoprotection.
- Hypo−/acromia (Fig. 14.30): This is usually due to excessive pressure in the application; however, it is unpredictable. Patients with history of hypo−/acromia with ablative lasers should be viewed with caution. Usually transient, for 3 to

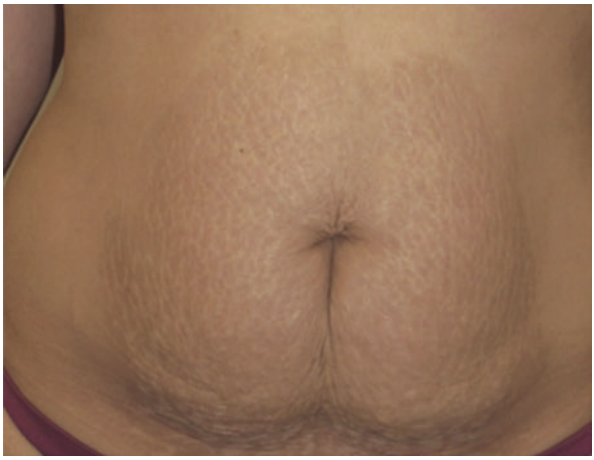

Fig. 14.29 Post-inflammatory hyperchromic after 1-month MMP® with glycosaminoglycans for stretch marks and flaccidity. (*Source*: Personal collection)

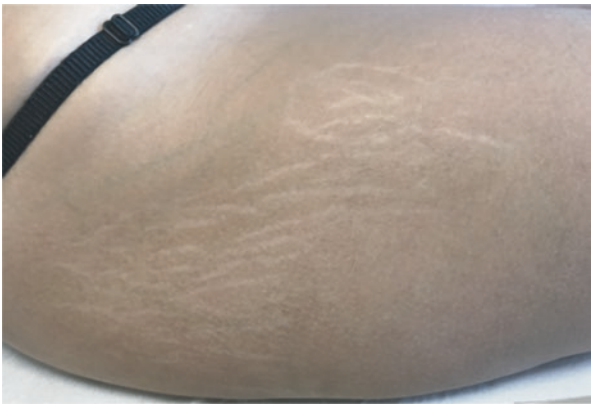

Fig. 14.30 Hypochromia after 15 days of MMP® for stretch marks with compounded glycosaminoglycans. (*Source*: Personal collection)

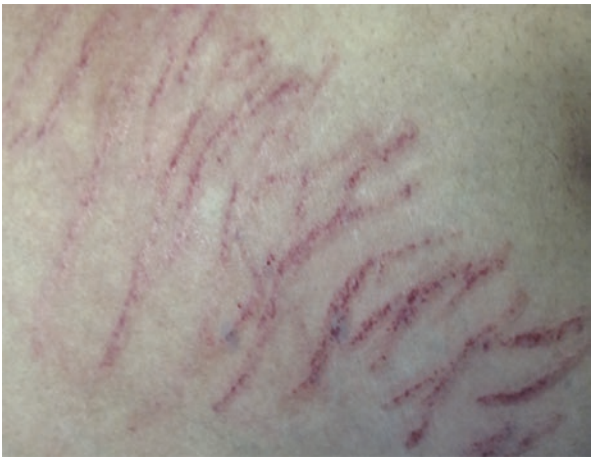

Fig. 14.31 Purple and ecchymosis in the immediate MMP® powder for stretch marks with manipulated glycosaminoglycans. (*Source*: Personal collection)

6 months. Treatment as vitiligoid lesion with 0.1% tarfic twice a day. Discrete application of 5FU with MMP® at the site should be considered for resistant cases after 6 months, with the risk of no response.

- Purpura (Fig. 14.31): Application with excessive pressure in patients with thin skin can generate purpura that can persist for up to 3 months. This should be considered in leukoderma patients, since the elderly have thinner skin and if the same pressure level used for young people is maintained, it will trigger purpura.
- Hematoma: Application with excessive pressure on the skin of the eyelid or stretch marks can trigger rupture of vessels with the formation of hematomas that soon leak out, leaving ecchymosis (Fig. 14.31) that can persist for 15 to 20 days.
- Reactivation of latent infection: The treatment of scars due to infectious diseases with MMP® is discouraged. The treatment of chickenpox scarring can trigger highly aggressive zoster reactivation at the site.

- Side effects of systemic drugs: Impotence has already been reported after the application of finasteride with MMP® in a patient who had only experienced decreased libido after oral drug.
- Dermographism: Should be questioned in the anamnesis. High-risk patients should be tested in a hidden area, e.g., retroauricular.

Conclusion

The technique presented in this chapter is new and promising in drug delivery. It combines the benefit of needling, active drug delivery and fractional treatment due to the distribution of needles, fractioning of greater ease of reepithelization in analogy to fractioning of a laser, and it does not emit heat, which reduces the risk of post-inflammatory hyperchromia, in addition to not having a coagulation barrier that impairs drug penetration.

Acknowledgments We thank the creator of the technique Samir Arbache, MD, and the collaborators Dirlene Roth, MD; Gustavo Alonso, MD; Aline Lissa, MD; Maria Teresa Pereira Soares, MD; Ana Paula Coelho, MD; and Ritha de Cássia Capelato Rocha, MD.

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Chapter 15
Protocols for Drug Delivery

Christine Rachelle Prescendo Chaves, Célia Luiza Petersen Vitello Kalil, and Valéria Campos

Introduction

The structure and composition of the stratum corneum (SC) is adequate for defense and protection; therefore there is significant limitation to the free permeation of most substances applied on intact skin, especially those with hydrophilic, macromolecular, and ionized characteristics. In order to allow permeation, there is a growing tendency to use methods or equipment that create micropores or that increase the spaces between cells in the stratum corneum. Multiple microporation techniques are available, including the use of lasers, microneedle radiofrequency, microneedling, electroporation, and iontophoresis, among others. What these procedures have in common is the increase of skin permeability through the temporary creation of aqueous channels or pathways whose microdimensions allow the penetration of even macromolecules. There is also an increase in the area available for skin permeation [1–3].

In dermatology, the purpose of creating these microchannels in the skin and increasing the permeation of active ingredients is to enhance treatments not only for rejuvenation but also to accelerate or improve results in the treatment of alopecia; hypertrophic, atrophic, and hypochromic scars; stretch marks; onychomycosis; actinic keratosis; vitiligo; and melasma. The use of drug delivery can also improve wound healing and hydration and decrease edema, erythema, discomfort caused by

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some of those equipment, and patient downtime. It is usually a simple, easy-to-execute method that brings comfort to the patient, which is a differential [3, 4].

Indications for Drug Delivery

Transepidermal/transdermal transport provides numerous benefits, such as noninvasiveness, avoidance of first-pass hepatic metabolism, enzymatic degradation, low bioavailability, reduction of systemic side effects, and lower cost of the active substances, since the required dosage is lower. Among the multiple methods used to alter cutaneous permeability and increase the supply of drugs of various physicochemical characteristics, each one has its peculiarities, such as the time the barrier function remains altered (Table 15.1), how the barrier function is altered, and the optimal properties of formulations applied to drug delivery. One of the benefits is that drug delivery can be extended over a long period, sometimes hours or even days (under occlusion), since the microchannels formed by the procedure may remain open and also because the skin coagulated by laser or radiofrequency functions as a drug reservoir [3, 5–7]. However, pretreatment with microneedle, lasers, among others, is not the only factor that affects the permeation rate of the active substances. Other factors, including the characteristics of the formulation, physical-chemical changes in the skin (there is a decrease in electrical resistance), and the micropore closure rate, are important to optimize transport by these methods [8]. Any changes in one of the four variables (active substances, formulation, occlusion, and the

Table 15.1 Methods used for favoring drug delivery[a]

Procedure	How it changes the barrier function and increases skin permeation	Drug delivery time
Microneedling	Micropunctures	At least 48 hours
Microneedled radiofrequency (MRF)	Micropunctures and pyramidal microscopic treatment zones (thermolysis)	At least 48 hours
Intense pulsed light (IPL)	Photothermal effect	15–30 minutes
Long pulsed Nd:YAG, non-ablative fractional Er:glass	Photothermal effect	8–60 hours
Ablative fractional Er:YAG and CO_2 laser	Photothermal and ablative effect	Until complete restoration of the barrier function (from 6 to 48 hours)

[a]Different methods to alter skin permeability and favor drug delivery. The effect responsible for modifying the barrier function and the average recovery time (it varies according to fluency, density, and additives of formulations for drug delivery) are described here

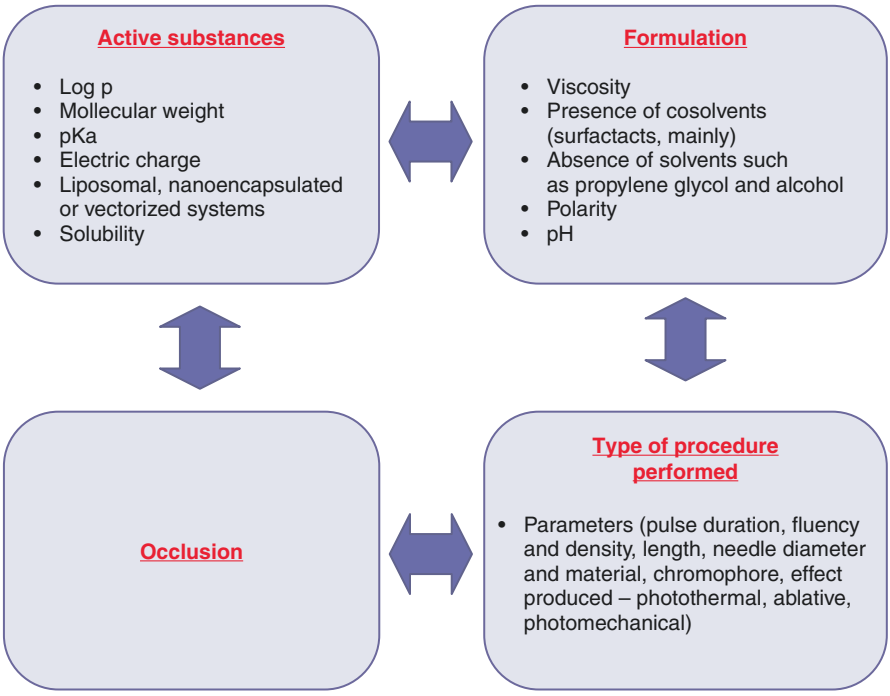

Fig. 15.1 Main factors that interfere in transepidermal/transdermal transport, favoring drug delivery. 1. Active substances. 2. Log *P*. 3. Molecular weight. 4. pKa. 5. Electric charge. 6. Liposomal, nanoencapsulated, or vectorized systems. 7. Solubility. 8. Formulation. 9. Viscosity. 10. Presence of cosolvents (surfactants, mainly). 11. Absence of solvents such as propylene glycol and alcohol. 12. Polarity. 13. pH. 14. Occlusion. 15. Type of procedure performed. 16. Parameters (pulse duration, fluency and density, length, needle diameter and material, chromophore, effect produced – photothermal, ablative, photomechanical)

method to change the barrier function – Fig. 15.1) will considerably influence the therapeutic response, since there will be change in the quantitative permeation [2–5, 7–10]. For each type of procedure performed, the active substances characteristics, vehicle characteristics, and occlusion should be considered in order to improve the partition coefficient of the drug with respect to the target tissue and in order to increase the flow rate of drugs into the tissue [3, 4].

For example, the most important precondition for iontophoresis is that drugs must be water-soluble and ionized; by definition, the technique allows the permeation of molecules that would not pass through the stratum corneum by passive diffusion. However, non-ionized and poorly water-soluble molecules can be adjusted within formulations for iontophoresis by modulating the physicochemical properties of the carrier, such as pH [3].

Formulation Requirements for Drug Delivery

The ideal formulation for drug delivery should be thermodynamically stable but have a partition coefficient that allows the drug to flow into the target tissue (it also depends on the properties of the tissue and on how it has been changed by the procedure), which will result in sufficient concentrations for the therapeutic action. It should also predict the transport pharmacokinetics of the active substances through the skin and how they are metabolized, since SC is not the only barrier to drug delivery, as all layers of the epidermis and dermis should be considered. In addition, the vehicle must have a viscosity that allows greater contact area between the drugs and the target tissue [2, 4].

As for the amount of product applied to the skin, there is a saturation point of the tissue above which larger amounts will not increase the permeation of the active substance. Ideally the drug delivery formulation should be reapplied repeatedly over time [4, 10].

Clinical and Microbiological Safety

Applying topical products to perform drug delivery can introduce immunogenic particles into the epidermis and dermis and potentially generate local or systemic hypersensitivity reactions. There are already reported cases in the literature, and since the market for drug delivery is growing, extra care should be taken by dermatologists [4].

One of the biggest causes of contact dermatitis are preservatives used in cosmetics, mainly isothiazolinones, parabens, and formaldehyde. It is estimated that 40% of contact dermatitis cases by cosmetic products are caused by the formulation's preservatives. Increased skin permeation of these preservatives may lead to an allergic granuloma reaction as described by Soltani-Arabshahi et al. in 2014 [11]. In addition to preservatives, essences are also considered major causes of contact dermatitis (major source of allergy in cosmetic products, around 50%) and should be avoided in the post-procedure. Another aspect that should be considered is the pH of formulations for drug delivery; the average physiological pH of the skin is usually in the range of 5.4–5.6 (with topographical variations), and it is important for maintenance of barrier function and innate defense against infections. The skin also has good resistance to pH variations, but after performing procedures that alter the barrier function, the pH may be modified. For instance, the pH of the skin surface returns to normal after 3 days of application of the CO_2 laser. Application of inappropriate products in the post-procedure may delay pH normalization or even modify it and lead to skin irritation and increased transepidermal water loss (TEWL). Products whose pH is less than 4 or above 7 increase considerably the risk of sensitization after the procedure [3–5].

Other substances, commonly present in cosmetics, already known as potential allergens, should also be avoided in formulations for drug delivery. Some examples are propylene glycol, petrolatums, benzophenones, amides and colorants [3, 4, 12, 13].

Another valid concern regarding the use of drug delivery for dermatological purposes refers to the risk of excessive drug absorption after a procedure, reaching relevant systemic concentrations. Today there is no concentration reference standard for the drugs applied, given the great variability that influences the permeation of active substances. However, it is known that procedures that remove stratum corneum (SC), such as ablative lasers, may favor the permeation of hydrophilic active substances into the bloodstream, since the dermis, which is basically hydrophilic, does not offer resistance to the free flow of active substances of the same physicochemical nature. Studies show that lipophilic active substances tend to form a reservoir in the skin and reach systemic levels more slowly and irregularly. Criteria such as fluency, density, length of needles, and drug concentration in the formulation, among others, should be carefully evaluated when applying the drug delivery technique. The use of occlusion and formulations of adequate characteristics favors the use of active substances in lower concentrations and the standardization of the technique [4, 13].

In relation to microbiological safety, Lee et al. (2016) [14] evaluated the risk of permeation of bacteria *Staphylococcus aureus* and *Pseudomonas aeruginosa* after treating the skin with non-ablative fractional Er:glass 1550 nm laser, and they observed no increase in risk of bacterial infection after laser application compared to intact skin. Nevertheless, issues regarding the risk of infection demand a greater number of studies concerning the need for sterile formulas in drug delivery, especially after ablative fractional laser.

Occlusion

An important point to consider is the level of hydration of the SC. The water content in the human SC is typically 15–20% of the weight of the dry tissue. With occlusion, the water content can get close to 400% of the weight of the dry tissue. Many of the clinical studies show that increased SC hydration is one of the mechanisms of action for increasing drug delivery. When the SC is fully hydrated (occlusion), it offers less diffusion resistance compared to non-occluded tissue [3, 4, 15, 16].

Recent studies have shown that the pores close within approximately 15 hours after microneedling without occlusion but this time can be extended by up to 72 hours when the pores are occluded with plastic film or an occlusive solution, which shows that occlusion also inhibits the recovery of function barrier [3, 4].

The increased hydration of SC favored by occlusion also brings benefits such as:

- Decrease in TEWL;
- Faster wound healing;
- Decreased edema;

- Reduction of erythema;
- Improved downtime.

The benefits of occlusion can be observed after a microneedling session with microneedles of 1.5 mm in length (Fig. 15.2a). An occlusive feature formula was applied to the right hemisphere of the patient before and immediately after the microneedling procedure, which was performed all over the face. The side receiving the occlusive formulation immediately after the procedure (Fig. 15.2b) is less red and less swollen; the dilated pores on the left side are visible, characterizing edema. Twenty-four hours after the procedure (Fig. 15.2c), with the patient keeping the use of an occlusive product in the right hemiface, there's a clear difference in edema and erythema between the two sides, showing the importance of TEWL reduction in the post-procedure period [4, 8, 10].

When formulations are applied without occlusion, there's significant evaporation of formulation components, and up to 50% of the applied weight may be lost.

The Vehicle

The effect of vehicle composition is much more pronounced on skin pretreated with laser, iontophoresis, electroporation, intense pulsed light (IPL), or microneedling as compared to treatment of intact skin.

The permeation of active substances occurs through two parallel and independent pathways: one through the intact skin around the microchannels and the other through the microchannels formed by the procedures. The permeation of each of these pathways is shown to be dependent on the formulation, and different flows are

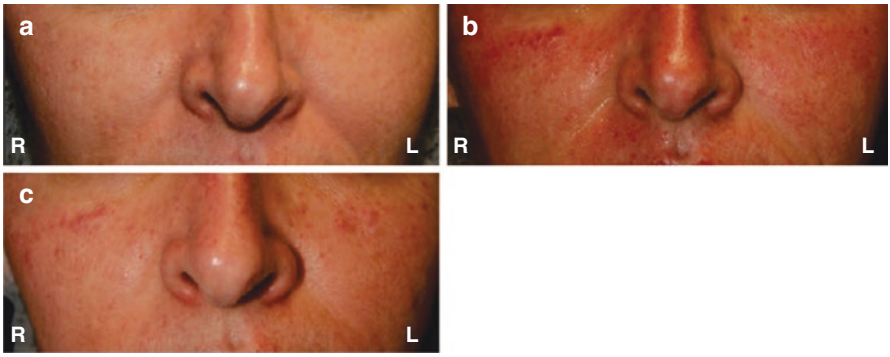

Fig. 15.2 Evaluation of the occlusive effect after microneedling procedure on the face. On the right side of the patient, a drug delivery formula with occlusive characteristics was applied before and immediately after the procedure. (**a**) Photograph of the patient before the procedure, (**b**) immediately after the procedure, and (**c**) 24 hours later. It is possible to observe a difference in edema and erythema between the two hemifaces

obtained according to the vehicle used. For instance, the value of the flow of active substances permeating through the microchannels is inversely proportional to the viscosity of the vehicle. Other characteristics such as occlusion, the presence of certain cosolvents, and physicochemical characteristics, such as the polarity of the vehicle, also influence the improvement of skin permeation of the active ingredients incorporated in the formulas for drug delivery [3, 4, 17].

Multiple physical methods allow the creation of micropores in the SC that often reach the deep dermis. This creates a different interface for transferring the drug into the tissue, and the rheological properties of the vehicle must be considered. The fluidity of the vehicle is directly related to the ability of the formulation to fill these micropores and make the active substances available for delivery into the tissue, and it is a precondition for efficient laser-assisted drug delivery, for instance, since it increases the contact surface between the drug/vehicle and the tissue [17]. After applying the CO_2 laser at 80 mJ/mb, Olesen et al. (2017) [17] demonstrated that 67% of the microscopic treatment zones (MTZs) were filled with a solution, while only 31% of the MTZs were filled with a cream and 25% of the MTZs formed were empty with this cream. The higher the fluency or the depth of the channels formed, the greater the importance of using a low viscosity formulation to decrease penetration resistance, especially in the permeation of hydrophilic active substances, which depend on the depth of the MTZs formed by the laser.

Filling the micropores with the formulation may also create a reservoir through which the drug diffuses into the medium for a longer period by maintaining a high concentration gradient.

The presence of propylene glycol or cream-based or ointment-based formulations greatly reduces the permeation of molecules, and it is the reason why increased fluency in ablative fractional lasers does not quantitatively increase the active substances permeating in MTZs. Solutions are usually the formulations with the best responses to drug delivery [1, 2, 6].

Another relevant aspect of the vehicle is what types of preservatives are used in its formulation. For greater clinical safety, ideally it is best to work with formulations that have neither preservatives, nor chelants, nor antioxidants, such as disodium EDTA (ethylenediamine tetra acetic acid) and BHT (butylated hydroxytoluene). Mineral and anhydrous vehicles, as well as injectable formulations, are alternatives that reduce the risk of dermatitis when using the drug delivery technique. In addition, mineral and anhydrous systems have the advantage of considerably reducing post-procedure burning and already provide an occlusive effect [4, 6, 11–13].

A mineral and anhydrous system can be composed of silicones – silicon polymers with hydrophobic characteristics which make them an important sealant against water, but not against gas exchange because of high permeability. When applied on the skin, they prevent TEWL loss, acting as a protective and moisturizing film.

Silicones have high flexibility and allow easy diffusion of gaseous molecules. Its inert nature (it does not react with other compounds spontaneously and it does not permeate the skin) guarantees a low risk of allergic reactions, even when applied on non-intact skin.

Active Substances [4, 15, 16]

Drug delivery is a cascade of molecular migration processes in which the active principle dissolves and partitions into multiple biological media with hydrophilic and lipophilic characters. Skin penetration is controlled by several parameters, and the main ones are affinity for target tissue, molecular weight, ionization, and hydrophilophilia characters. To determine the hydro-lipophilicity of an active substance, it is common to accept Log *P*, a logarithm for the partition coefficient, which means that the active substance behaves in a single electrical state and is in equilibrium between two non-miscible solvents. Generally, the more positive the Log *P*, the more lipophilic the active substance. And what is its importance for the dermatological application after the procedures? Studies show that not all available active substances have good permeability, even when the barrier function is altered due to their properties. Choosing active substances with ideal physicochemical characteristics will provide a better result, but it depends directly on how the procedure alters the barrier function and which type of active substance is favored (Table 15.2). For example, when the procedure of choice for treating androgenetic alopecia is microneedling associated with peptide drug delivery, the drug of choice should be the base peptide (Log *P* 0.21), whereas if the procedure chosen is ablative fractional laser, such as Er:YAG 2940 nm, the active substance of choice should be sulfate peptide (Log *P* −0.79 – Table 15.3).

The charge (electrical state) of a drug can affect the physicochemical properties, such as solubility and permeation through the skin. Therefore, the pH of the formulation may directly affect the transepidermal permeation rate, since each drug has a pKa value (which we can simplify as the pH at which 50% of the active substance is in the non-ionized form) and the pH of the formulation will determine whether the substance is ionized or not. As a rule, non-ionized active substances have better skin permeation; however there are active substances that are much more soluble in the ionized form than in the non-ionized form, and, therefore, they not only permeate much faster but also show great increase in the amount of molecules that they are able to permeate, minimizing the effect of their low partition coefficient.

Table 15.2 Procedures for drug delivery and types of active substances whose permeation is favored

Procedure	Favored active substances
Microneedling	Lipophilic, amphiphilic, liposomal, nanoencapsulated, and vectorized
MRF	Lipophilic, amphiphilic, liposomal, nanoencapsulated, and vectorized
IPL	Lipophilic, liposomal, nanoencapsulated, and vectorized
Q-Switched	Hydrophilic
Non-ablative fractional laser	Lipophilic, liposomal, nanoencapsulated, and vectorized
Ablative fractional laser	Hydrophilic, liposomal, nanoencapsulated, and vectorized

Table 15.3 Physical-chemical characteristics of drugs used for drug delivery[a]

Substance	Molecular weight (g)	Log *P*	Solubility in water (mol/L)	Cutaneous permeability Log Kp (cm/s)	pKa
5-Aminolevulinic acid (ALA)	131.131	−1.15	0.951	−9.80	4.05
Methylaminolevulinate (MALA)	145.158	−0.18	0.183	−7.92	7.15
Methotrexate	454.447	−0.32	0.0001	−10.39	4.7
5-Fluorouracil	130.077	0.13	0.02	−7.73	8.02
Ascorbic acid	176.124	−1.42	31	−8.54	4.7
Acyclovir	225.20	−1.04	0.005	−8.78	2.27 e 9.25
Lidocaine base	234.33	2.50	0.00003	−6.12	8.01
Botulinum toxin type A	149322.7				
Diphenylcyclopropenone	206.24	3.22	0.000002	−5.22	−8.3
Minoxidil base	209.25	0.21	0.538	−6.70	4.61
Minoxidil sulfate	289.31	−0.79	1.2	−6,75	4.6
Tretinoin	300.44	5.01	0.00068	−3.66	4.2
Caffeine	194.19	0.08	0.214	−7.53	10.4
Hydrocortisone	362.46	1.89	0.0023	−7.37	11.05
Ingenol mebutate[b]	430.53	2.40	0.00205	−7.52	12.09[b]
Prednisolone	360.44	1.74	0.00681	−7.35	13.9
Tranexamic acid	157.21	0.27	0.322	−8.68	4.3 e 10.6
Triamcinolone	394.43	1.21	0.0147	−7.88	11.75[b]
Amorolfine	317.51	4.57	0.000002	−4.35	6.6

Source: Courtesy of Dr. Maria Lionzio, pharmacist

[a]Physicochemical characteristics of some drugs commonly used for drug delivery.
[b]Strong acid.

The pKa value of the active substances can alter the pH of the skin and cause skin irritation. For example, benzoic acid derivatives, whose pKa is less than or equal to 4, cause skin irritation within 24 hours. The same results are seen when using active substances with pKa greater than 8. Based on several studies, it is ideal to use in a drug delivery formulation active substances whose pKa is in the range of 4–8 (Table 15.3). However, if this is not possible, the concentration of the drug in the formulation should be decreased in order to reduce skin irritation and promote the induction of resistance or accommodation (decreased inflammatory response and increased synthesis of ceramides 1). It is also possible to replace the active substance with a liposome or nanoencapsulated derivative. In addition to decreasing irritation, we might observe an increase in the number of molecules that permeate freely, besides improving the reach of these drugs in greater depths. The postulated mechanisms for reducing skin irritation by liposomes and nanoencapsulated active substances include hydration of the epidermis and sustained release of drugs, thus preventing the accumulation of toxic concentrations of the active substances in the skin.

As for the concentration of the drug in the formulation, studies demonstrate that increasing the concentration of the active substance leads to an increase in the dose-dependent permeation. However, saturated or highly concentrated solutions lead to tissue saturation, and no increase in penetration is observed. Also, regarding the concentration of active substances, the safety of the high flow of active substances should be considered, since it may increase the risk of irritation or systemic permeation.

Presence of Cosolvents [4, 15, 16]

Cosolvents, also known as absorption promoters or accelerators, are agents that interact with SC components, increasing skin permeability in a temporary and reversible manner. They can be classified according to their chemical structure, for example, surfactants (ethoxydiglycol, polysorbate 80, sodium peptide sulfate), fatty acids (linoleic acid, lauric acid), esters (isopropyl myristate), amides (dimethylacetamide, urea), hydrocarbons, and phospholipids, among others.

Cosolvents modify the structural organization of the lamellar lipids of the SC, making it more permeable and increasing the partition coefficient of the drugs. The action of these permeants is potentiated along with other systems that alter skin permeation, such as microneedling, lasers, and electrophoresis. They show synergistic action when there is increased penetration of drugs into the skin, and they provide benefits such as:

- Increasing the opening time of the pores formed in microneedling;
- Loading active formulations into the skin (they favor the partition coefficient);
- Promoting lateral diffusion of active substances beyond the procedure area;
- Increasing the interlamellar spaces created by the photomechanical effect on Q-switched lasers [9];
- Favoring the solubility of the active ingredients in the formulation and increasing the amount of molecules that permeate freely into the skin.

When comparing several categories of cosolvents, such as chemical permeants, surfactants (polysorbate 80, ethoxydiglycol, sodium peptide, hydrogenated castor oil) generally cause greater disorganization of the lamellar lipids in the SC and create higher levels of skin absorption than other classes, such as terpenes (menthol, camphor) and solvents (alcohol, propylene glycol), and therefore several studies use sodium lauryl sulfate (LSS) associated with lasers. Combining LSS and photomechanical waves increases the effectiveness of drug delivery by creating wider pores and delaying the recovery of the barrier function. It is possible to observe greater expansion of the lacunar spaces and the secretion and lamellar bodies in the granular layer (when compared to the use of aqueous solution). However, the irritative potential of LSS, which also interacts with the viable epidermis causing cytotoxicity and irritation, should be considered, and other surfactants, such as ethoxydiglycol, should be chosen for the formulations.

In addition, the presence of solvents such as propylene glycol seems to decrease the flow of active substances into the skin [6]. Under constant conditions of active substances and parameters of the procedures in which only the propylene glycol concentration varies in the vehicle, transepidermal/transdermal transport proved to be a function of vehicle composition, where the lowest flow was obtained with a pure propylene glycol solution and the highest flow in the solution without that solvent. Flow differences reached an order of 40 times.

The presence of the cosolvents may increase the solubility of the incorporated drugs. The increase in cutaneous permeation is directly related to how much the drug is soluble and available for drug delivery.

Protocols for Drug Delivery [3, 4]

Preparation of the Skin

Protocols for laser drug delivery usually recommend low energy and low densities for best results, so the incidence of side effects is low, but it is important to remember that the most common side effects to lasers are usually pigmentation disorders, especially post-inflammatory hyperpigmentation (PIH). However, the triggering factors remain unknown; it is assumed that thermal damage to keratinocytes and melanocytes during treatment increases the inflammatory response during the healing process. The incidence of PIH is greater than 23% in patients with phototypes I to III, and it may reach 50% in patients with type IV. Several attempts have been made to reduce the PIH after treatment with lasers, including avoiding sun exposure, use of bleaching formulations before and after the procedure, application of sunscreen, choosing conservative energy parameters, and using equipment to cool the skin during the application of the procedure to protect the epidermis from the heat generated by the laser [18].

When relevant, it is best to start, if possible, 30 days in advance. The commonly used formulas are based on hydroquinone, tretinoin, and fluorinated corticoid, such as fluocinolone acetonide. It is believed that steroids suppress cellular activity, leading to an inhibitory effect of melanin synthesis. Short-term prophylactic use of oral prednisolone has been adopted to reduce the risk of inflammatory reactions and pigmentary changes in Asians. Topical application of corticosteroids after laser is also an option to prevent PIH by reducing the inflammatory process. However, post-procedure use is controversial as it may interfere with the healing process and increase the risk of infection.

More modern whitening substances with less side effects may be adopted before and after treatment. The active ingredients include glycolic acid, mandelic acid, and ascorbic acid (in concentrations of 15%), in combination with 4-hexylresorcinol (0.5–1.5%), tranexamic acid (1–5%), and nicotinamide (up to 5%). Studies today show the positive effect of combining moisturizer formulations with depigmentants,

Table 15.4 Antioxidants used in adjuvant therapy for melasma[a]

Class	Active substances	Usual daily dose
Polyphenols	Picnogenol	50–150 mg
	Polypodium leucotomos	250–1000 mg
	Resveratrol	50–200 mg
	Pomegranate	200–400 mg
Carotenoids	Astaxanthin	4 mg
	Lycopene	5–20 mg
	Lacto-lycopene	30–70 mg
	Zeaxanthin	2–4 mg
	Lutein	5–10 mg
	Beta-carotene	10–30 mg
Antiglycation agents	Alpha-lipoic acid	100–300 mg
	Carcinin	100–300 mg
Superoxide dismutase (SOD)	Dimpless®	40 mg
Others	Coenzyme Q10	50–100 mg
	PQQ (pyrroloquinoline quinone)	5–20 mg

Source: Courtesy of Ana Raquel Medeiros, pharmacist
[a]Main nutraceuticals of dermatological use available on the market in Brazil for adjuvant therapy of melasma.

since they reinforce the barrier function and reduce or prevent irritation in the post-procedure period.

To clean the area, one can choose a mild, sulfate-free soap and an inorganic sunscreen (zinc oxide-based and/or titanium dioxide-based). These measures help decrease the chances of irritation common in acid treatment and increase patient compliance. For patients with melasma, the positive effect of antioxidants and oral nutraceuticals as adjuncts to treatment is described. In this case, carotenoids, polyphenols, antiglycation agents, and others may be used (Table 15.4).

When the procedure of choice is CO_2 laser, antiviral prophylaxis is recommended for 5 days, usually starting 24 hours before the procedure. The drug of choice generally is 200 mg acyclovir administered five times a day, totaling a dose of 1 g daily.

Procedure Day

Analgesia [19]

Topical anesthetics decrease pain during outpatient procedures and allow a variety of treatments to be performed without the need for anesthetic infiltration; however, as the number of dermatological procedures in the office continues to grow, it is important to know the indications, pharmacological mechanisms, appropriate methods of application, and safety profiles of the anesthetics available on the market.

To be effective, topical anesthetics need to cross the SC and affect the nerve endings in the dermis. The SC thickness determines how much the anesthetic can permeate through SC and have greater or lesser potency, which is why the effectiveness is higher in mucosae, for example. The anesthetics commonly found on the market are lidocaine, tetracaine, benzocaine, and prilocaine.

Some techniques may be used to increase the permeation and action of topical anesthetic, such as the use of an exfoliant or degreasing the skin with acetone. The use of heat or occlusion also significantly increases the ability of the anesthetic to permeate the SC. The addition of epinephrine in the formulation induces vasoconstriction and increases the local duration of the effect.

The inadvertent application of topical anesthetics can cause serious complications, even leading to death. Long-term application; inappropriate use of high concentrations; application to extensive areas, damaged skin, inflamed areas, or mucous membranes; occlusion; and methods to increase permeation may increase the risk of cardiotoxicity and toxicity to the central nervous system. The initial symptoms of anesthesia-induced toxicity include dizziness, numbness around the mouth and metallic taste, diplopia, and tinnitus. Many adverse reactions also appear to be related to the inclusion of epinephrine within the anesthetic mixture. Erythema or pallor and edema are common adverse reactions to the use of topical anesthetics.

For most dermatological procedures, the use of a topical anesthetic is sufficient for patient comfort; however ablative fractional laser, when used more aggressively, for example, may require other complementary methods. Because of the effect on the deep dermis of these lasers, the time of topical application of lidocaine should be at least 60 minutes (for low concentration anesthetics) to achieve uniform anesthetic effect on the deep dermis. During this type of procedure, a cooling device may also be used on the skin. Oral sedation with benzodiazepines or non-steroidal analgesics such as ketorolac tromethamine may also be used. Despite these measures, the use of blockade with infiltrative anesthesia is often necessary during very painful procedures.

Application Instructions

Apply a generous layer of topical anesthetic in the area to be treated. Allow 40–60 minutes (depending on the extent of the area and the type of procedure). Apply only to intact skin (avoid inflamed, injured, or eczematous areas). Avoid contact with eyes in order to prevent eye injury.

Thoroughly remove the product before the procedure. This measure prevents drug delivery from the anesthetic.

Tips:

- The use of lidocaine is a relative contraindication for patients with hepatic disorders, since its metabolism happens in the liver. Avoid in patients with hepatic failure;

- Limit the use of tetracaine and prilocaine in patients using metamoglobinemia drugs;
- Attention to the amount of product applied, the total surface area covered, the thickness of the SC, and the duration of application;
- For treatment of large areas, limit the application of the product to selected areas (hot spots) that are more sensitive, and abandon the application of topical anesthesia in less sensitive areas;
- The combination of topical anesthesia with oral or analgesic anxiolytics and refrigerated devices decreases the use of topical anesthesia and brings more safety to the procedure;
- Keep the patient under supervision during the time of anesthesia.

Drug Delivery Procedure

Immediately after the procedure, apply the chosen product on the area and massage for better absorption. Use an occlusive dressing or occlusive formula to increase hydration, improve healing, and reduce edema and erythema.

In the case of IPL, the application of the formula for drug delivery should be done immediately after the procedure. There is no need to occlude the area.

Maintenance at Home

Differences in pre- and postoperative care may influence a lower incidence of adverse effects associated with procedures that modify the permeability of the skin. The use of formulations in the postoperative period is an important tool as more invasive procedures, such as the CO_2 laser, are used. The treatment consists of improving the re-epithelization of the skin, besides reducing edema, erythema, and dehydration, among others, and reducing the risk of IHP. The use of petrolatum (petroleum jelly, mineral oil, paraffin) during the first 24 hours after the procedure may contribute to the increased incidence of colloidal milium, which is why it is rarely used.

It is important to tell patients to avoid sun exposure before and four days after treatment.

Post-treatment care includes cold compresses and thermal water used frequently during the day, twice daily washing with mild, sulfate-free soap, and reapplication of drug delivery formulation for three days. The crusts formed when using aggressive parameters in ablative lasers are shown to delay absorption by decreasing partitioning and subsequent diffusion of drugs from the vehicle to the tissue. Therefore, the use of drug delivery after the formation of these crusts does not seem to have greater benefits.

After crusting, start the ointment for another four days, followed by the use of solar filter with sun protection factor (SPF) of, at least, 30 for, at least, one month after crusting to prevent PIH, since sun exposure increases epidermal thickness and melanin synthesis, which leads to changes in the appearance of the skin. The reason why it is not recommended to apply the sunscreen immediately after the procedure is because the product may cause irritation and permeate, acting as a drug delivery and possibly causing a sensitization.

The recovery of the skin using laser drug delivery takes 24–48 hours, but when done with aggressive parameters, it can take from seven to ten days. After this period, use of depigmentants that also have anti-inflammatory action, such as 4-hexylresorcinol, methimazole, Belides®, TGP 2 peptídeo®, tranexamic acid, esters of vitamin C, kojic acid, phytic acid, and nicotinamide, can be initiated.

Illustrated Uses of Drug Delivery (Figs. 15.3, 15.4, 15.5, 15.6, 15.7, and 15.8)

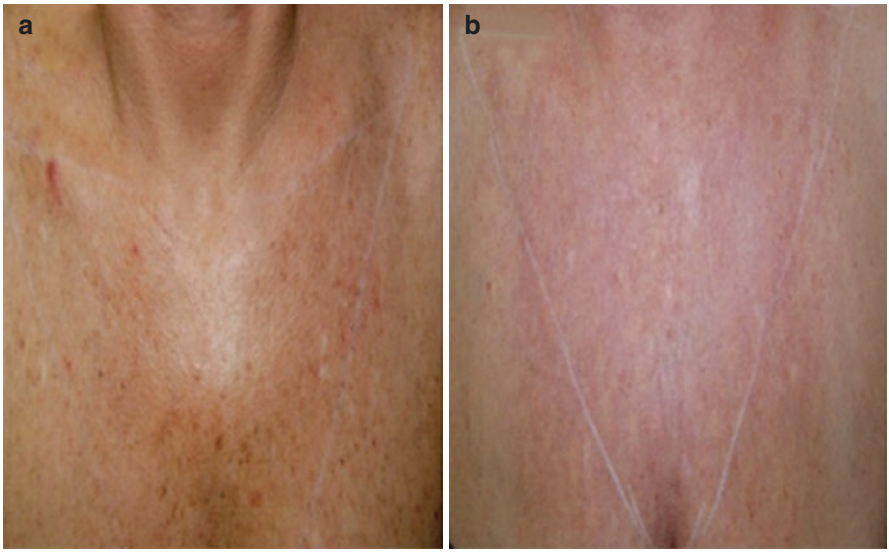

Fig. 15.3 Combination of microneedling with cosmeceuticals formulation (Juvenile® 2%, PhytoCellTec Malus Domestica® 0.5%, Cell to Cell® 2%, Homeostatine® 5%, hyaluronic acid 2.5%, and fluid anhydrous serum q.s.p.) for treating rejuvenation of the cervix. (**a**) Before treatment and (**b**) 30 days after two microneedle sessions (Dr. Roller® of 1.5 mm) combined with drug delivery. The general rejuvenation showed clinical improvement of 28% (p 0.05), as well as positive results in texture, poikiloderma, and general whitening of the area

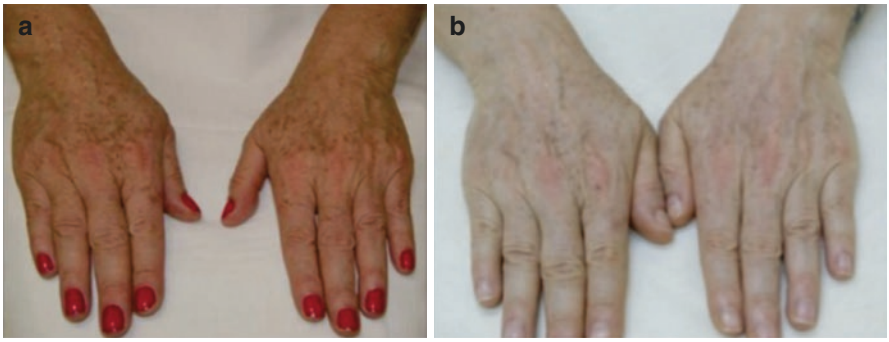

Fig. 15.4 Combination of microneedling with whitening activations in hand photorejuvenation treatment (tranexamic acid 0.4%, 4 hexylresorcinol 1.5%, alpha bisabolol 1%, belides 2%, and peptídeo TGP-2 2%, in fluid serum anhydrous). (**a**) Before treatment and (**b**) 30 days after the last microneedling session (Dr. Roller® of 1.5 mm) combined with drug delivery. Besides the whitening of the area, it is possible to observe improvement in the texture and quality of the skin. (Adapted from: Kalil et al. [20])

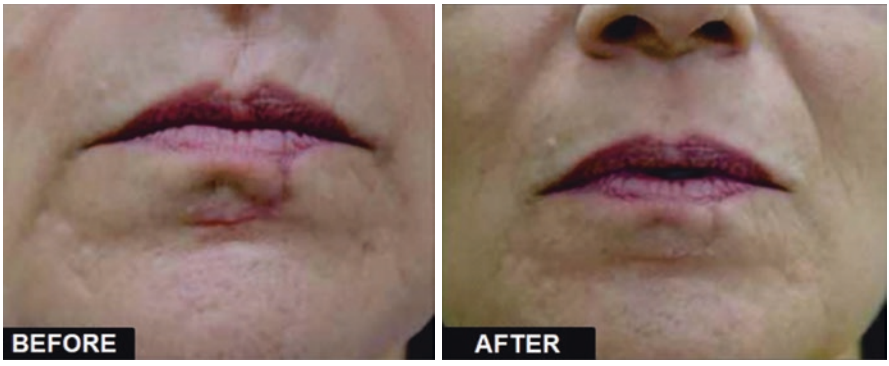

Fig. 15.5 Perioral scar treated with Er:glass 1340 nm laser and drug delivery (Hyaxel 3%, rhamnose 3%, IDP2 peptídeo 1.5%, Arct Alg 1%, Hydroxyprolisilane 6%, Ethoxydiglycol 3%, Anhydrous Serum QSP: before (left) and after (right) six sessions, with excellent response. (Adapted from: Kalil et al. [3])

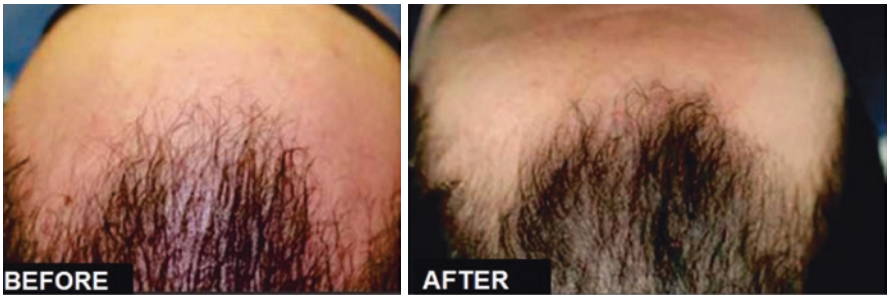

Fig. 15.6 Androgenic alopecia treated with six Er:glass 1340 nm laser sessions with drug delivery of minoxidil: before (left) and after (right). (Adapted from: Kalil et al. [3])

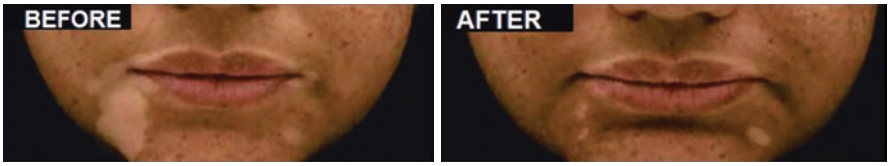

Fig. 15.7 Vitiligo treated with fractional CO_2 laser followed by desonide: before (left photo) and after three sessions (right). (Adapted from: Kalil et al. [3])

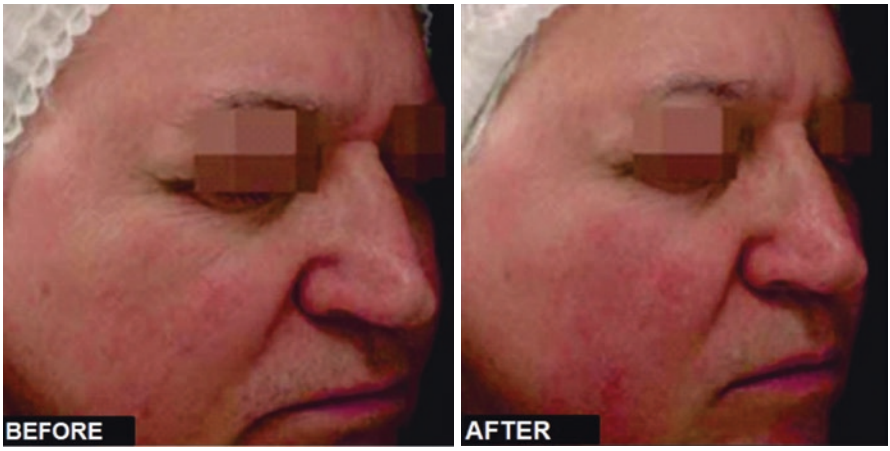

Fig. 15.8 Patient treated for facial rejuvenation with fractional CO_2 laser followed by vitamin C in drug delivery: before (left) and after (right). (Adapted from: Kalil et al. [3])

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