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New developments in the treatment of aesthetic problems with electroporation

Konstantina Theodoropoulou[1,*], Efstathios Rallis[1], Vasiliki Kefala[1]

[1]University of West Attica, School of Health and Care Sciences, Welfare, Department of Biomedical Sciences, Aigaleo, Greece.

***Corresponding author**
Vasiliki Kefala, University of West Attica, School of Health and Care Sciences, Department of Biomedical Sciences, Aigaleo, Greece.
Email: valiakef@uniwa.gr

Abstract
In the present paper we study the literature and research done by notable researchers, around the science of transdermal administration, the most recent scientific developments in enhancing skin permeability using third generation technologies. The purpose of this search is to find the latest transdermal methods through electrically assisted transdermal absorption systems to address aesthetic problems, specifically with the electroporation method. Electroporation allows quick and deep penetration of active ingredients, through the "electropores" promoting the ability to channel ingredients such as vitamins, minerals, amino acids, etc. to the desired point. In this way, effective, targeted, and uniform distribution of the active water-soluble substances of small and high molecular weight is achieved, in deeper layers of the skin tissues. As a result of this whole process, the electroporation method is an additional weapon in our quiver for dealing with and improving aesthetic problems.

KEYWORDS
electroporation, transdermal delivery of substances, aesthetic problems, newer developments in aesthetic problems, transdermal methods through systems, electrically assisted transdermal absorption

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1. INTRODUCTION

Electroporation is a technique that has been used for several years at a research level, but in recent years it is finding more applications, replacing the hitherto known methods, such as iontophoresis, ultrasound, etc. First, the human skin is investigated, its function is recorded and analysed to understand the mechanism of its permeability modification. Detailed information is then listed on the mode of action, the effectiveness, and the contribution of the method to maintaining its effectiveness on a case-by-case basis, as well as, with the electroporation method, we manage to address the needs of our skin, and which are those needs that can be covered up. Information on their diagnosis and treatment is recorded,

considering the necessary precautions to protect the person to whom it is applied. Finally, various methods of increasing transdermal absorption with the electroporation method are compared and its advantages are recorded.

2. HUMAN SKIN

In the epidermis, a constant renewal of its cells works on the skin. The mechanism and dynamics of renewal are of great interest and are proof of the inability of cosmetic products to remain in a constantly changing cellular system. The renewal results from the cells of the basal layer which regenerated by successive mitosis at a rate of 90% and when mature they move to the granular layer, with the final destination of the stratum corneum being rejected as keratinocytes. The duration of cellular maturation is on average 28 days, but in pathological conditions, cell lifespan can be accelerated. The skin is composed of three primary layers:

1. the epidermis
2. the dermis and
3. the hypodermis.

The epidermis has five layers that are structurally, firmly connected to each other. The epidermis layers from the outside to the inside are:

1. stratum corneum
2. stratum lucidum
3. stratum granulosum
4. stratum spinosum
5. stratum basale [1-4].

3. PERMEABILITY, PENETRATION, AND ABSORPTION OF SUBSTANCES THROUGH THE SKIN

The skin prevents:

- the entry and exit of water and electrolytes from the body,
- the entry of micro-organisms and harmful chemicals and
- the penetration of ultraviolet radiation.

However, many substances penetrate the skin at an insignificant rate. Human skin is poorly permeable to water but relatively impermeable to aqueous solutions and ions. The greatest resistance that determines the absorption of substances from the skin is the permeability of the stratum corneum. The stratum corneum consists of an array of three consecutive passive barriers. The first barrier is formed by the hydrolipid mantle, which covers the outer part of the epidermis. The stratum corneum forms a second barrier and is considered stronger than the first. And the third, which is the thinnest barrier, is formed by the Rein membrane. Absorption of substances through the skin is a passive function with varying rates of distribution and absorption [5-12]. It is also described by Fick's laws of diffusion. Substances enter through the stratum corneum, penetrate the dermis and the deepest layers of the skin, and finally enter the circulation from the capillary blood vessels.

Thus, the various substances, depending on their type, enter the skin:

1. through keratinocytes,
2. from the intercellular substance of the stratum corneum and
3. from the appendages of the epidermis.

The stages of absorption of a substance from the skin are:

1. Distribution of the substance between the stratum corneum and the carrier of a substance.
2. Diffusion of the substance through the stratum corneum.
3. Distribution of the substance between the stratum corneum and the live epidermis.
4. Diffusion of the molecules of the substance in the live epidermis
5. Entry through capillary blood vessels.

The total transdermal absorption of a substance is possible that different mechanisms are simultaneously involved. The route of a substance penetration, its penetration mechanisms are closely dependent on the size of the molecule, i.e. their molecular weight, from the initial state of the substance i.e. gas, liquid or solid and by its lipophilic, hydrophilic, or amphiphilic character [5-7].

TABLE I.
Factors affecting transdermal absorption [3, 7, 13-16].

A. Physiological factors	B. Physicochemical factors
1. Skin condition	1. Nature of the carrier of a substance
2. Anatomical region	2. Area hydration levels
3. Perfusion of the skin	3. Temperature
4. Skin age	4. Physicochemical properties of the substance
5. Temperamental factors	5. Use of penetration accelerators
	6. Substance pH
	7. Substance – skin interactions
	8. Concentration of substance

3.1 Optimization of the transdermal absorption

Different methods have been developed on a scope of minimizing the stratum corneum mechanics that prevents the rise of transdermal

absorption of active cosmetics substances [9, 15-32].

TABLE II.
Methods for optimising transdermal absorption

Modifying stratum corneum	Bypassing stratum corneum	Electrical driven methods	Substance – carrier interaction	Particles and Carriers (Substance transportation systems)
Moisturize	Micro needling	Iontophoresis	Pre meds	Liposomes
Penetration enchantment	Noninvasive jet injectors	Electrophoresis	Thermodynamic activity	Microemulsions
Stratum corneum removal	Invasive mesotherapy	Ultrasound	Ion pair	Lipid nanoparticles
		Magnetophoresis	Melting systems	
		Photo – mechanic waves		
		Thermophoresis		

4. ELECTRICAL DRIVEN METHODS

In the first case we have iontophoresis. The basic principle of iontophoresis is the application of a low-frequency electric current (typically <0.5 mA/cm2 of skin) in a pulsed or continuous wave to drive charged molecules of an active substance into the skin. The number of charged molecules crossing the barrier is directly related to the applied current. The devices contain a positive and a negative pole. In the second case we have the electrophoresis method.

Higher voltage is applied for a few milliseconds to disrupt the structural organization of lipids in the stratum corneum and thereby facilitate passive diffusion. Temporary hydrophilic pores (water pathways) are created across the barrier due to instantaneous lipid structural rearrangement mechanism. They facilitate the movement of macromolecules, combining diffusion, electrophoresis and electroosmosis mechanics. Electropuncture acts mainly on skin to change its permeability to increase the delivery of the active substance. On the other hand, iontophoresis acts directly on the molecule of the active substance itself to penetrate the skin. In the third case we refer to the ultrasound method. This method uses high or low ultrasound frequency. Ultrasound frequency intervenes dynamically by changing the lipid structure of the stratum corneum by forming empty cavities, when they collapse the interstitial spaces are increased in the lipid bilayers facilitating the passage of substances. In the fourth case we have the magnetophoresis method. According to this enhancement technique, magnetic fields are used to facilitate the active substance penetration of the molecules into the skin. The intensity of the magnetic field increases the diffusion flow of the substance through the epidermis. In the fifth case we have the photomechanical waves method. Also known as laser generated pressure waves. The photomechanical wave creates a mechanical oscillation in the stratum corneum that increases permeability. The last electrically driven method is thermophoresis. Thermophoresis is implemented with chemical substances, with thermopunching, with radio frequencies and with lasers. The skin temperature increasement causes greater blood flow, resulting in increased permeability through the stratum corneum and capillary walls [15,17,19,21,25-28,31-34].

5. ELECTROPORATION

Electroporation is the creation of temporary pores on the epidermis through the application of an electrical pulse. The pulse is generated by an alternating electric current and is transferred to the skin through a special electrode. With this method, effective, targeted, and uniform distribution of low and high molecular weight active substances is achieved. (Hyaluronic acid, Collagen, Vitamin Complexes, Amino Acids and Proteins) in deeper layers of the skin. The penetration depends on the sinusoidal pulse current produced by the device, its intensity, and the duration of the application.

Electroporation:

1. creates new pathways for the penetration of substances and
2. drives the substance molecules into the skin.

As a result, the barrier created by the keratin layer to water-soluble and many hydrophobic substances is dissolved. The created pores are maintained for 15 to 20 seconds and have a maximum length of 1.5 millimetres. Through them, the channelling of active ingredients to the specific parts of the skin we want to improve their appearance is facilitated [21,27,32,35-37].

5.1. Advantages, disadvantages of electroporation

Advantages:

- The transport mechanism can be applied equally well to every cell regardless of the cell cycle and life type.
- With this method, effective, targeted, and uniform distribution of the active substances is achieved.
- The whole process is biochemically & biologically non-toxic.
- Enhances drug delivery to the skin for gene therapy, wound healing, development of large permeable areas in the stratum corneum, and

immediate skin regeneration after electroporation.

Disadvantages:

- involve transient damage to the cell membrane for the substance to be transported into the cells. Consequently, collateral damage leading to some small-scale cell death is considered inevitable. This is referred to as "toxicity" of the physical therapy.
- The lack of quantitative supply and cell death where they occur at high electric fields.
- Pain and muscle contraction at the application site.
- Possible damage to volatile substances [27,31,36,37].

5.2. Electroporation Requirements

Before using electroporation, pay attention to the following:

- Electroporation Device
- Cosmetics Products
- Updated information for:
  - the safety of the device,
  - its effectiveness
  - its ease of handling
  - the cost-result relationship [38,39].

5.3. Electroporation Substances

Human skin applies a protective function by creating and imposing physicochemical limitations on the type of penetrant that can cross it. The method of electroporation has been successfully used to enhance the skin permeability of molecules with:

- Different lipophilicity and size (i.e. small molecules, proteins, peptides, and oligonucleotides) including biopharmaceuticals with a molecular weight greater than 7 Kda.
- Proteins, enzymes, amino acids, vitamins, minerals, peptides, plant extracts, polysaccharides, urea, glycerine, water, etc.
- Non-toxic.
- In their nano, micro or macro molecular structure, their percutaneous absorption varies.
- Meso-cocktails. Meso-cocktails are fortified serums, usually without preservatives and fragrance, with a very high concentration of active ingredients for a more immediate effect.

These active substances are provided in the form of a mixture, ready for use, they have a thin fluid texture for optimal absorption and are specially designed for use with electroporation devices [11,21,27,31,37-43].

6. AESTHETIC PROBLEMS - ELECTRPORATION APPLICATIONS

For the face:

- wrinkles (endogenous, expression, photoaging)
- discolorations, freckles, spots, scars, acne marks
- epidermal slackness
- swelling
- loss of hydration, elasticity, and toning.

For the body:

- cellulite (edematous, fatty, fibrosclerotic)
- in areas with increased local fat deposition (abdomen, arms, thighs, buttocks)
- local lipodystrophy
- epidermal slackness
- stretch marks.

There are specific treatment protocols where each professional electroporation device and professional cosmetics company adapts its products. These special protocols are differentiated according to the different needs of each skin, the device and the cosmetic substance that will be used, as well as the study of the problem that needs to be addressed. They usually listed into the following categories:

- treatments for photoaging
- hydration treatments
- treatments for antioxidant activity
- treatments for skin regeneration
- anti-aging treatments
- firming treatments
- straightening treatments
- lipolysis treatments [1-3,21,43-47]

7. DISCUSSION

We choose the Electroporation method because:

- the transdermal administration of substances has the potential to improve the therapeutic effect, maintaining the supply of the active substance to the selected tissue at a good level, reducing to a minimum the risks of complications.
- allows a faster and deeper penetration of the active ingredients into the tissue, when with iontophoresis, ultrasound, or other methods of electrically assisted transdermal absorption, the treatment would take longer and be less effective.
- electrical pores are created along the entire surface of the stratum corneum, and their number is 500 times greater than the iontophoresis penetration pathways.

- electroporation, whether used alone or in combination with other enhancement methods, expands the range of active substances (small to macromolecules, lipophilic or hydrophilic, charged, or neutral molecules) that can be administered transdermally.
- through the electropores, it is established the possibility of directly channeling a quantity of substances with vitamins, with minerals, with amino acids and enzymes, to the targeted point of the body where the problem is observed.
- treatment protocols are adapted according to the device, the aesthetic problem, and the substances to be used to achieve the optimal effectiveness of a cycle of treatments.

8. CONCLUSION

With electroporation an effective, targeted, and uniform distribution of the active substances, of low and high molecular weight, is achieved in deeper layers of the skin tissues. With this method, electroporation offers the most modern and sophisticated beauty treatments in the field of cosmetology for the treatment and improvement of aesthetic problems.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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