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Iontophoresis: principles and applications[1]

Iontoforese: princípios e aplicações

Eddy Krueger[a], José Luiz Claudino Junior[b], Eduardo Mendonça Scheeren[c], Eduardo Borba Neves[d], Eduardo Mulinari[e], Percy Nohama[f]

[a] PhD candidate, Universidade Tecnológica Federal do Paraná, Curitiba, PR - Brazil, e-mail: kruegereddy@gmail.com
[b] Graduate, Unidade de Ensino Superior Vale do Iguacu, União da Vitória, PR - Brazil, e-mail: joseluiz.claudino@gmail.com
[c] PhD, professor, Pontifícia Universidade Católica do Paraná, Programa Pós-Graduação em Tecnologia em Saúde, Curitiba, PR - Brazil, e-mail: eduardo.scheeren@pucpr.br
[d] PhD, professor, Universidade Tecnológica Federal do Paraná, Programa de Pós-Graduação em Engenharia Biomédica, Curitiba, PR - Brazil, e-mail: borbaneves@hotmail.com
[e] MSc, Universidade Federal do Paraná, Curitiba, PR - Brazil, e-mail: edumulinari@gmail.com
[f] PhD, professor, Universidade Tecnológica Federal do Paraná, Curitiba, PR - Brazil, e-mail: percy.nohama@gmail.com

Abstract

Introduction: Iontophoresis is a noninvasive technique used to increase transdermal penetration of substances through the skin layer (epidermis, dermis and hypodermis) in a controlled manner. Technological advance in recent decades have provided reduced cost of equipment needed for implementation, which allowed for the expansion of this technique. **Objective**: The aim of this paper is to present the state of the art on iontophoresis, ranging from the atomic characteristics of the ion formation to the current applications of the technique. **Methods**: Were researched papers from databases: *IOP publishing*, *ScienceDirect*, *Pubmed*, *Springer*, *IEEE Xplore*, *Google Scholar* and books with keywords iontophoresis, ions, topical applications between 1967 and 2010. **Results**: Were selected (number of papers and database) 1 *IOP Publishing*, 1 from *ScienceDirect*, *Central*, 1 from *Springer*, 2 from *PubMed*, 11 from *IEEE Xplore*, 35 from *Google Scholar*, and 15 books, totaling 66 references and websites with nationally marketed electrotherapy products. **Conclusion**: Iontophoresis is suitable for applications such as acetic acid (calcific tendinitis and myositis ossificans),

[1] Study conducted at the Rehabilitation Engineering Laboratory (Laboratório de Engenharia da Reabilitação, LER), Federal Technological University of Paraná (Universidade Tecnológica Federal do Paraná, UTFPR), Curitiba Campus, Paraná.

calcium chloride and magnesium sulfate (control of musculoskeletal spasms), dexamethasone (inflammation), lidocaine (inflammation of soft tissues), zinc oxide (rheumatoid arthritis). It is also used in cosmetic applications with devices attached to the skin and for eye treatment aimed at specific tissues of the eye, providing a treatment option for various eye diseases, reducing the complications secondary to traditional methods of treatment. The advantages are the significant increase in the release and control of therapeutic agents, including drugs with high molecular weight. The disadvantages of iontophoresis are the complexity of the drug release system and prolonged exposure of the skin to an electrical current.

Keywords: Iontophoresis. Treatment. Topical applications. Electrical stimulation. Drug infusion.

Resumo

Introdução*: A iontoforese é uma técnica não invasiva utilizada para aumentar, de forma controlada, a penetração transdermal de substâncias através das camadas da pele (epiderme, derme e hipoderme). O avanço tecnológico nas últimas décadas proporcionou uma redução no custo dos equipamentos necessários à sua aplicação, o que possibilitou a expansão dessa técnica.* ***Objetivo****: Apresentar o estado da arte sobre iontoforese, abrangendo desde as características atômicas da formação do íon até as atuais aplicações da técnica.* ***Métodos****: Foram pesquisados artigos das bases de pesquisa:* IOP publishing, ScienceDirect, Pubmed, Springer, IEEE Xplore, Google Scholar *e livros com os unitermos: iontophoresis, ions, topical applications entre os anos de 1967 e 2010.* ***Resultados****: Foram selecionados (número de artigos e base de pesquisa) 1 da* IOP Publishing, *1 da* ScienceDirect, *1 da* Springer, *2 da* PubMed, *11 da* IEEE Xplore, *35 do* Google Scholar *e 15 livros, totalizando 66 referências, além de websites com produtos comerciais nacionais de eletroterapia.* ***Conclusão****: A iontoforese é indicada para aplicações como de ácido acético (tendinite calcificante e miosite ossificante), cloreto de cálcio e sulfato de magnésio (controle de espasmos musculoesqueléticos), dexametasona (inflamação), lidocaína (inflamação de tecidos moles), óxido de zinco (artrite reumatóide). Também é utilizada em aplicações cosméticas com dispositivos aderidos à pele e em tratamento ocular visando tecidos específicos do olho, oferecendo uma forma de tratamento para diversas doenças oculares, diminuindo as complicações apresentadas em métodos clássicos de tratamento. As vantagens são o significativo aumento na liberação e controle de agentes terapêuticos, incluindo fármacos com alto peso molecular. As desvantagens encontradas na iontoforese são a complexidade do sistema de liberação do fármaco e exposição prolongada da pele a uma corrente elétrica.*

Palavras-chave*: Iontoforese. Tratamento. Aplicações tópicas. Estimulação elétrica. Infusão de medicamento.*

Introduction

Iontophoresis (1) is a noninvasive technique used to increase the penetration of ions through the skin layers (2). An electrolytic solution is infused with controlled voltage and/or charge (3), with the aid of two electrodes connected to the skin, the anode (positive electrode) and cathode (negative electrode).

With the advancement of microprocessor and microcontroller technology, electrotherapy devices configured for iontophoresis application decreased in size and became more affordable due to low production costs (4). Iontophoresis can be used as a noninvasive intraocular drug application and can also simulate natural hormone secretion (4). The clinical application of iontophoresis may promote reaching of therapeutic indices, providing a treatment option for various eye diseases, reducing the complications secondary to classical methods of treatment (5).

The main advantages of iontophoresis are a significant increase in the release of various types of therapeutic agents, including drugs with high molecular weight, in addition to providing better control of the release of these agents (3). The disadvantages are: difficulty stabilizing the therapeutic agent in the application vehicle, complexity of the drug release system, and prolonged skin exposure to an electric current (6).

The aim of this paper is to present the state of the art on iontophoresis, ranging from the atomic

characteristics of the ion formation to the current applications of the technique.

Methods

The information search was conducted using the following databases: *IOP publishing, ScienceDirect*, *Pubmed*, *Springer*, *IEEE Xplore*, *Google Scholar*, as well as in books on the topic. The selected preferred language was English, with the following keywords: iontophoresis, ions, topical applications. The inclusion criterion was articles which mainly addressed the application of iontophoresis in animal tissues. Studies not in accordance with the scope of the article were excluded. After performing the database searches, the abstracts were read and duplication was eliminated. Of the selected studies, information on the following topics was extracted: iontophoresis, ions and topical applications.

In addition to the articles, available books were selected from the libraries at the Federal Technological University of Paraná and the Pontifical Catholic University of Parana about iontophoresis, and related subjects such as basic biochemistry. The studies used were published between 1967 and 2010. Moreover, a search for nationally marketed electrotherapy products that had the option for iontophoresis (or merely Galvanic Current) and electroporation was performed.

Results

The article was written considering one article retrieved from *IOP Publishing*, one from *ScienceDirect, Central*, one from *Springer*, two from *PubMed*, 11 from *IEEE Xplore*, 35 from *Google Scholar*, and 15 books, totaling 66 references. The search for nationally marketed electrotherapy products that had the option for iontophoresis (or merely Galvanic Current) and electroporation identified the following brands: Ibramed®, Advice®, Quark®, and KLD®.

State of the art

First observations of matter

For a better understanding about iontophoresis, the basic structure of the ionized atom is presented, merging with historical works on the use of iontophoresis. Medical books from the sixteenth century show that the personal physician of Queen Elizabeth I, William Gilbert (1544–1603), was one of the most important authors in the field of electrotherapy (7). Gilbert is considered the father of modern electrotherapy and wrote over 20 studies on the subject, including the book, *De Magnete*, in which the foundation of electrotherapy, including iontophoresis, was described (7). All existing matter in the universe is composed of mass (amount of matter) and has microscopic structures called atoms (from the Greek άτομο, ά = no; τομο = cut, split). Greek philosophers, such as Leucippus of Miletus and Democritus of Abdera, (400 BC) stated that the atom was indivisible (8). Centuries later, John Dalton (1766–1844), took up this hypothesis and postulated theories about the indivisibility of the atom. It is currently believed that an atom has tens of subunits as the results of practical experiments (9). In order to study the human being, the increasing sequence of structures is accepted: [1] atom, [2] molecule, [3] cell, [4] tissue, [5] organ, [6] organism (10, 11).

Differentiation of electrical charges

In his studies, Benjamin Franklin (1706–1790), realized that, by causing friction between two bodies, they acquired opposite electrical charges. At the time, Franklin attributed this to an "electric fluid". Currently, it is known that every atom has a number of protons equal to the number of electrons, causing electrical neutrality. After the friction of two bodies, one receives more electrons, becoming negatively charged, while the other is positively charged (12, 13, 14). Charles François de Cisternay du Fay (1698–1739) (15) proved that charges of the same polarity repel each other; charges of opposite polarities attract one another (13, 16, 17).

Every atom has a valence shell, its outer orbital containing electrons. Depending on the number of electrons in this orbit, the atom gives or receives electrons according to the octet law: “many of the atoms reach electrical stability when they have eight electrons in their valence shell” (9). Therefore, every ionized atom with a number of protons greater than the number of electrons is called cation, and when the situation is reversed, the atom is called anion (16, 18).

Giving or receiving electrons usually occurs in covalent or ionic bonds; in covalent bonding two atoms share electrons through their valence shell, both tending to receive electrons, characteristic of nonmetals, semimetals and hydrogen. In ionic bonding, there is the transport of electrons from one atom to another, one giving and the other receiving. In this type of bonding, metals tend to donate electrons, while nonmetals, semimetals and hydrogen tend to receive them (15).

Atomic structures and characteristics

In the nineteenth century, Joseph John Thomson (1856–1940), with a cathode ray tube, showed that atoms were divisible. In the same century, Eugen Goldstein (1850–1930) discovered the proton (15). In the twentieth century, Ernest Rutherford (1871–1937) developed the atom model that is currently in use. Decades after Rutherford`s evidence, James Chadwick (1891–1974) suggested the existence of the neutron in the atomic structure (9). The atom has atomic subunits such as protons, neutrons, electrons and other particles. The proton mass is approximately 1.6×10^{-24}g, and the charge is 1.6×10^{-19} Coulombs (15, 19). Neutrons have a similar mass compared to the proton, with neutral electric charge. Electron have 9.1×10^{-28}g, and a charge of -1.6×10^{-19} C (12, 20).

Niels Bohr (1885–1962), in the early twentieth century, proposed that electrons were distributed in orbits (K , L , M , N , O, P and Q) around the nucleus (8). Arnold Johannes Wilhelm Sommerfeld (1868–1951) inserted sublevels (s, p, d, f , g, h, ...) to the electron layers (9, 21). Every atom has atomic subunits. With the modification of the number of structures present in an atom, there is the formation of differentiated structures (22). Dimitri Ivanovich Mendeleev (1834–1907) and, later (in the twentieth century), Henry Gwin-Jeffreys Moseley (1887–1915) modeled the periodic table in order of increasing atomic number (Z) (9).

The Skin

The skin covers and protects the body, separating the internal environment of the outer environment. It is the largest organ of the human body, representing around 16% of body weight (23). The human integumentary tissue is divided into: [1] epidermis, [2] dermis and [3] hypodermis. The surface of the epidermis is called the *stratum corneum* (24). The *stratum corneum* (Figure 1) is an important component of the skin layers, responsible for preventing loss of body fluids, and for blocking the entry of exogenous substances (25).

The physicochemical properties of the skin enable percutaneous absorption of topically applied medications; however, most of the medications used need to overcome the barrier imposed by the *stratum corneum* (26) in order to guarantee their pharmacological effects (27). The three pathways that a medication uses to overcome the *stratum corneum* are: [1] intracellular, where medications diffuse around corneocytes, [2] transcellular, where medications diffuse directly through the corneocytes, and [3] via appendices, an alternative route for medications that diffuse through the hair follicles, sebaceous and sweat glands (4).

Iontophoresis

Iontophoresis, also called ionophoresis, electrophoresis or cataphoresis (29), is a technique used to enhance transdermal penetration (30) of substances through the application of electric current (2, 31).

In addition to constant stimulation, the main waveform used in iontophoresis is quadratic, as shown in Figure 2. Applications can be made either with continuous or pulsed current (32). Iontophoresis is based on the principle enunciated by Du Fay (15), in which charges with the same signal repel and charges with opposite signals attract, facilitating the penetration of ions through the skin (33).

Another technique similar to iontophoresis is electroporation, which is used to open the pores of the lipid membrane for the application of transdermal medications, similar to iontophoresis (34). The main difference is that electroporation uses high voltage (≈ 70 to 400 V) during short application periods (milliseconds) (35), whereas iontophoresis ranges up to a few tens of volts (36).

Reverse iontophoresis (38) aims to attract substances out of the skin (39, 40), as shown in Figure 3. One practical application of this technique is the classical test for assessment of sweat conductivity in people suspected of having cystic fibrosis. In this case, the procedure is called pilocarpine® iontophoresis (41).

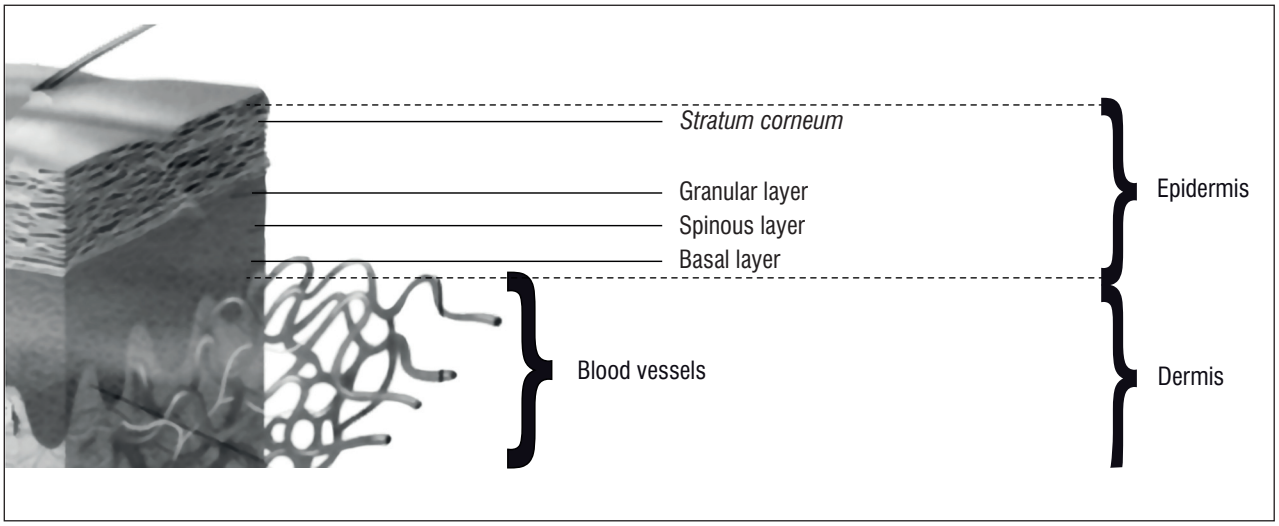

Figure 1 - The *stratum corneum* and the epidermis layer
Source: Modified from Saúde Total (28).

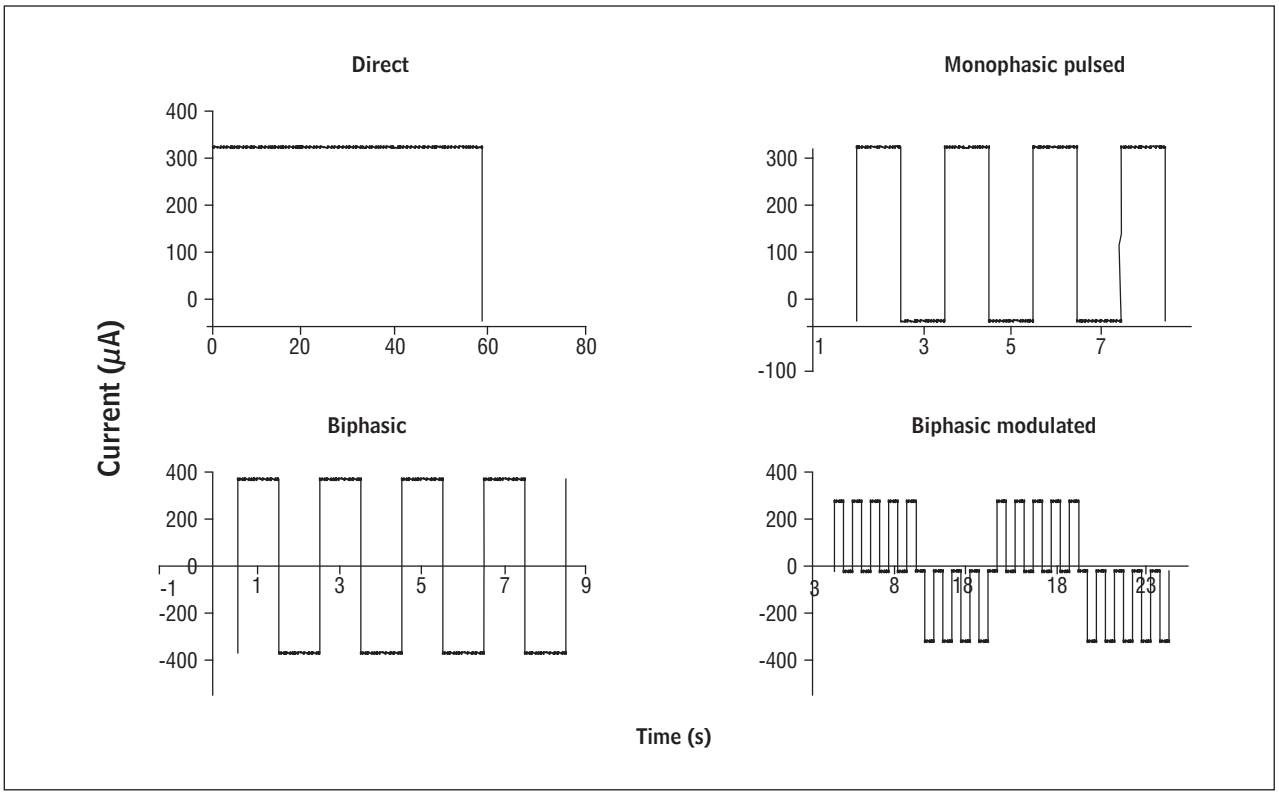

Figure 2 - Types of quadratic waveform used in iontophoresis
Source: Modified from Ching et al. (37).

According to Chorilli et al. (6), a medication of positive polarity should be positioned next to the positive electrode. When electric current flows through the circuit, the medication will be moved away from the electrode, causing it to penetrate through the skin into the desired location. Other mechanisms involving iontophoresis in medication delivery into cells have been studied, such as electroosmosis (42). Electroosmosis is caused by solvent flowing from the anode to the cathode. This flow occurs because the

skin is negatively charged, mainly due to the presence of amino acids in cell membranes (43). The impulse of solvent movement is transferred to the neutral molecules present in the system; thus, the solvent flow, or electroosmotic flow, makes it possible to neutral molecules to be liberated by iontophoresis through the anode (33).

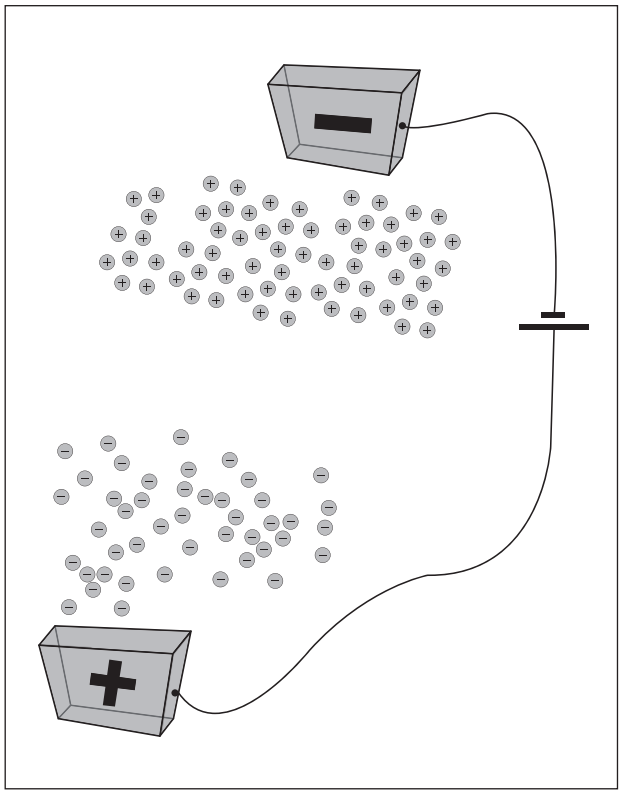

Figure 3 - Illustration of reverse iontophoresis effect over ionized substances. With application of a continuous current, substances with opposite polarities attract to each other

Source: Authors.

Samuel George Morton (1799–1851) conducted an experiment on his own arm, in which graphite powder was placed in contact with a positively charged electrode, followed by application of electric current. The result was the appearance of spots on the skin where the application was made. Morton, in the nineteenth century, describes that the reaction occurred due to the migration of ions from the positive electrode to the negative, in other words, the basic principles of iontophoresis (4).

The use of iontophoresis is variable in length of application and electric intensity for each substance, using a predefined voltage or electrical current (44), controlling the amount of transdermal transfer of both positive (cations) and negative (anions) ions (2, 33). In addition to the reduction of size and cost of electrical stimulators, currently equipment that enables iontophoresis can be adhered to the skin in the same manner as traditional transdermal devices (Figure 4) and nicotine patches (4), except with a primarily cosmetic application (1), as shown in Figure 5 .

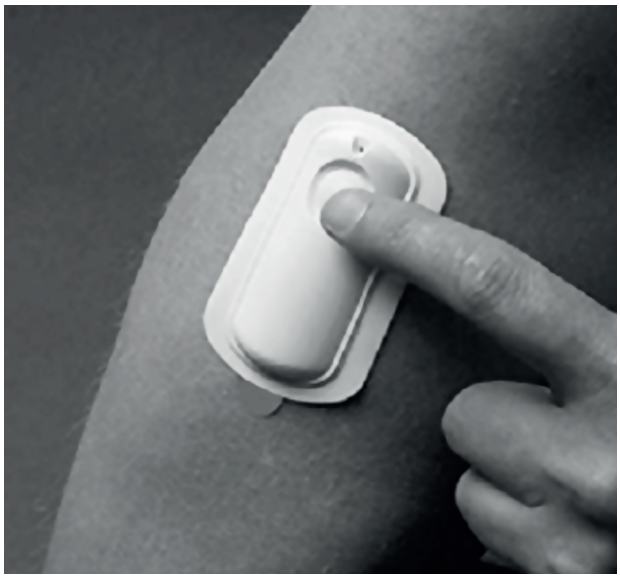

Figure 4 - Iontophoresis device applied to the forearm with digital activation through push-button button

Source: Subramony et al. (45).

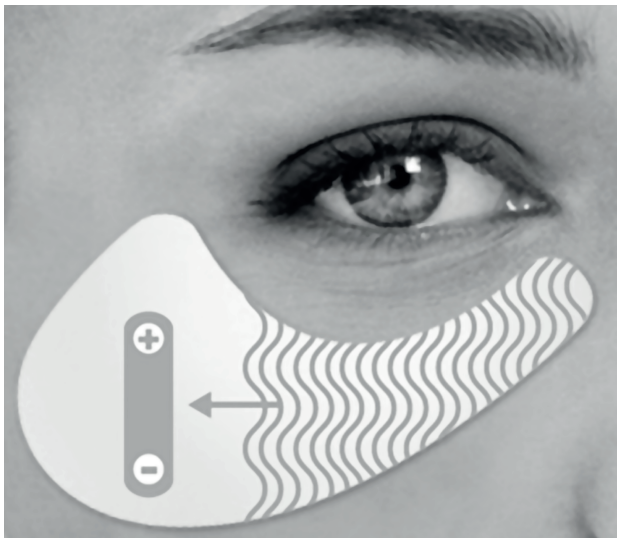

Figure 5 - Iontophoresis adhesive used adhered to the skin for cosmetic purposes

Source: Modified from mapfremulher.com.br (46).

Iontophoresis can be applied through adhesives or electrical stimulators. Jensen and Li (47) developed a device that allowed for constant iontophoretic application at frequencies up to 50kHz (quadratic waveform), with a configured work cycle of 20%, 50% and 80%. The current supplied to the electrical stimulator was 50-500 μA with variable voltage from 0.5 to 5 V. Ching et al. (37) developed a low cost electrical stimulator for the application of iontophoresis (48). The output current varied from 1–300 μA with waveforms that could be: [1] continuous (DC), [2] pulsed continuous, [3] bipolar and [4] pulsed bipolar. The provided amplitude reached 36 V.

The use of transdermal pathway as a gateway for medications into the body is comfortable and efficient, providing an alternative to the classical routes of medication administration, such as injectable and parenteral. It provides a treatment requiring a lower frequency of administration, proper absorption and easy removal and promotes greater patient compliance to treatment (6). As simple and interesting as the use of transdermal mechanisms may seem, their development and implementation requires extensive knowledge about the factors that affect their use, such as barriers imposed by the skin, skin penetration, site of action, medication stability and dosage (6).

In Brazil, there are some brands that work commercially with the development and sale of products that enable electrical therapy, with the options of iontophoresis application (or Galvanic current only) and/or electroporation (49, 50, 51, 52). Table 1 shows some devices available in the national market and their basic specifications.

Iontophoresis and its applications

Since the 1930s, the use of iontophoresis is reported as means for the application of various medications. Among them are: [1] acetic acid for treatment of calcific tendinitis and myositis ossificans; [2] calcium chloride and magnesium sulfate for control of musculoskeletal spasms; [3] dexamethasone for inflammation; [4] lidocaine for soft tissue inflammation; [5] zinc oxide for acute joint pain, such as damage from rheumatoid arthritis (53).

Because it is a non-invasive system for transport of molecules and because it has no restrictions regarding the number of applications, iontophoresis is used for ocular treatment by Behar-Cohen et al. (54). Using its electromotive action, iontophoresis-based treatment, whose practice is illustrated in Figure 6, has the ability to carry various types of medications to different eye tissues, without any risk to the integrity of the patient's eye (54).

Table 1 - National commercial devices with the option for applying iontophoresis/electroporation
(To be continued)

Description	Brand	Frequency	Option	Amplitude/Intensity
Sonopeel (52)	Ibramed®	DC	MGa	0 - 990 μA
Striat (52)	Ibramed®	DC	MGa	0 - 400 μA
			Ga	0 - 20 mA
Neurodyn Esthetic (52)	Ibramed®	DC	PM	10 - 990 μA
Sonopulse II Combined Therapy (52)	Ibramed®	£	HV	1 - 250 V
Sonopulse II Combined Therapy (52)	Ibramed®	£	HV	1 - 250 V
Crio Thermo Máster (50)	Advice®	*	Iontophoresis	*
Dualpex 071 (51)	Quark®	DC a 8 Hz	Ga	80 mA
Diapulsi 990 (51)	Quark®	DC	Ga	60 mA

Table 1 - National commercial devices with the option for applying iontophoresis/electroporation (Conclusion)

Description	Brand	Frequency	Option	Amplitude/Intensity
Endophasys NMS 0501 (49)	KLD®	8 kHz	Ga	80 mA
Sonophasys EUS 0503 (49)	KLD®	8 KHz	Ga	*

Note: The products presented provided other currents. Here only specifications for use in iontophoresis were focused. DC = Continuous current; MGa = Galvanic microcurrent; Ga = Galvanic current; PM = polarized microcurrent; HV = High voltage current; £ = two single-phase low frequency twin pulses of 1 Hz to 100 Hz; * = Data not found.

Source: Authors.

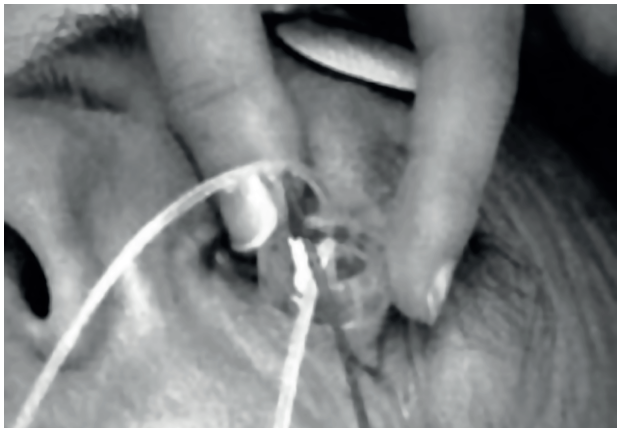

Figure 6 - Use of iontophoresis for ocular treatment
Source: Modified from Fialho et al. (5).

In an experimental study (44), the use of gentamicin sulphate with iontophoresis was tested on rabbit cornea. In this study by Frucht-Pery et al. (44), after application of gentamicin sulfate associated with iontophoresis, the rate of gentamicin penetration was influenced by the intensity of the current and/or the length of iontophoresis application. The major disadvantages presented in this type of treatment (eye) are possible burns resulting from repetitive electrical contact of electrodes near the eye (5).

Behar-Cohen et al. (54) evaluated the application of iontophoresis with ocular application of dexamethasone in rats with parenteral administration of the same drug. The results revealed that treatment with iontophoresis produced the same treatment efficacy as parenteral application, but without presenting systemic adverse effects, because it was a topical application.

A study conducted by Say et al. (32), used iontophoresis with the drug histamine bicloridate (1/10.000) as a palliative treatment for hemophilia patients in order to promote absorption of bruises and analgesia. It should be noted that in some cases, histamine is irritating to the patient's skin. In this case, the simple application of galvanizing properties provided by iontophoresis appeared amenable to treatment.

Iontophoresis can also be used for clinical analysis, as in the procedure used for evaluating the sweat conductivity described by Mattar (55). First, cleaning with distilled water and drying of the skin is performed, after which 2.5 cm x 2.5 cm copper electrodes are put on the skin. Gauze soaked in a solution of pilocarpine nitrate is attached below the positive electrode (anode) and a sulfuric acid solution of 4 mEq/L is attached below the negative electrode (cathode). A current from 2 to 5 mA is then applied for five minutes. After application, the skin is cleaned and dried again for application and fixation of filter paper, which remains in place for 30 - 60 minutes, then it is sent for laboratory analysis of sodium and chlorine.

The technique demonstrated by Belda and Reginato (56) used ionization with potassium iodide followed by 2% sodium salicylate ionization. Sixteen applications in patients with leprosy were performed three times a week, over a period of twenty to fifty sessions. Eight patients had reversal of paralysis and normalization of gait. In these cases, the duration of paralysis varied from one month to a maximum of two years.

Geloid fibroedema, popularly and mistakenly called "cellulite" is a frequent and aesthetically relevant dysfunction, especially for the female population (57). It is described (58) that treatment using iontophoresis and galvanization (use of electric current without pharmaceuticals) shows remarkable results in the treatment of cellulite reduction.

Research conducted by Zanin et al. (59) aimed to apply abdominal electrolipophoresis, together with iontophoresis associated with a pharmaceutical consisting of turmeric gel. The experiment aimed to evaluate the lipid profile and levels of fat in the abdomen, before and after applications. The study was conducted in eighteen women aged 21 to 51 years old, who were sedentary and without dietary restriction. The data collected showed satisfactory results regarding the use of electrolipophoresis along with turmeric in decreasing the levels of the lipid profile (LDL), as well as the effective decrease of subcutaneous adipose tissue.

A new technique for administering pharmaceuticals involved in ionized microcapsules (60), iontophoresis could control the transdermal movement of these encapsulated substances as it does with the usual pharmaceuticals (61).

Iontophoresis and application parameters

Zakzewisk et al. (62) evaluated iontophoresis with four types of waves in the reduction of blood pressure in rabbits. Iontophoresis was administered with the pharmaceutical captopril, an angiotensin converting enzyme inhibitor. The frequency of electrical stimulation was 10 Hz – 50 kHz, work cycle of 10% – 50%, and output current of 0 – 10 mA. The types of stimuli used were: [1] continuous, [2] pulsed continuous [3] trapezoidal, [4] pulsed biphasic. The stimulatory pattern that resulted in greater reduction in blood pressure was the continuous pulsed wave. Pulsed biphasic waveform on the other hand had the poorest results.

The results by Kim et al. (42), after application of a mannitol solution with NaCl associated with iontophoresis on skin flaps of rats, showed that even after applications with four and eight hours duration, no significant pH changes occurred in the solution. Even in situations in which the initial pH was 7.4 (neutral) or 3.4 (acid), iontophoresis application did not destabilize the pH of the solutions utilized.

Zakzewski et al. (63) evaluated iontophoresis with captopril for lowering blood pressure in rabbits. It was shown that 20-minute applications had similar results to those in the group that continued to receive the application of iontophoresis for two hours. These results indicate that iontophoresis reaches its maximum efficiency after a few minutes; however, after application, the effect of the iontophoresis maintains a low blood pressure for more than 90 minutes.

According to data by Carvalho et al. (64), eighteen patients with a clinical diagnosis of low back pain were randomly divided into two groups. The group named group [1] underwent iontophoresis application with dynamic Bernard currents (monophasic). Group [2] was subjected to dynamic Bernard currents with iontophoresis associated with the pharmaceutical, hydrocortisone. Upon completion of the tests, it was found that both techniques significantly reduced back pain.

A study conducted by Heidemann and Rosas (65) used [1] galvanic current (continuous) and [2] diadynamic (monophasic sinusoidal) together with diclofenac sodium applied to the positive (anode) and negative (cathode) poles. The continuous current had more efficient results when the pharmaceutical was applied to the positive pole.

Yan et al. (66) showed that the application of iontophoresis with alternate waveform at a frequency of 1 kHz, at intensities of electrical current tolerable to humans (2-5mA), had similar results in transdermal ion movement when compared to a constant current application at 0.2 mA .

Esteves Junior et al. (3) applied a treatment based on iontophoresis associated with an endogenous vasodilatory peptide (CGRP) on skin flaps of four groups of rats. Electrodes coupled to an electrical stimulator were used, where treatment was based on the application of a direct current amplitude of 4 mA for 20 min, with an interval of two days. The results showed that, on the seventh postoperative day, there was no significant difference in the area of necrosis between the control group and the group that received treatment with iontophoresis. The area of necrosis in the group receiving treatment came to be 20% lower than that of the control group.

Iontophoresis can be used for insulin delivery through the dermis (67). Bustelo et al. (68) tested the interaction of subcutaneous insulin dissolved in 25 mL of buffer solution with iontophoresis. Electrodes with Ag-ClAg (silver, chlorinated silver) were used with constant current at 1.2 mA for 30 minutes in crural region (point where insulin was applied) in rabbits. During the 30 minute application, the glycemic index was attenuated compared to the control group, but ten minutes after iontophoresis application, the level of glucose in the experimental and control groups became equal. The results of this research showed that there was viability in the application of

iontophoresis on insulin action, but studies of the effects that iontophoresis causes in the tissue with iontophoresis application should be evaluated.

Iontophoresis has also been applied in a closed loop system, where the level of pharmaceutical to be activated through the skin was controlled by feedback obtained through the patient's perspiration (45). Wascotte et al. (38) used reverse iontophoresis (extracts substance through the skin) as an alternative to analysis of endogenous molecules (as for diagnosis of renal failure) and correlated this with blood samples. The potential of iontophoresis to measure urea and potassium during hemodialysis was analyzed between 10–360 minutes of application (increments of 30 in 30 minutes). Urea presented a r^2 of 0.93 at 90 minutes of application and potassium concentration had a r^2 of 0.91 at 120 minutes of application. These results suggest that non-invasive monitoring of urea and potassium seems to be an alternative method for diagnosing renal failure and during hemodialysis. With the same technique of reverse iontophoresis, Sun et al. (40) used reverse iontophoresis with carbon nanotubes for the construction of a glucose biosensor.

Jain et al. (69) tested the effect of iontophoresis with application of glibenclamide (a pharmaceutical for the treatment of type II diabetes) in the skin of pigs. Iontophoresis had a cathodic application where the current density was 0.5 mA/cm^2 for eight hours. It was compared with tissues which did not have iontophoresis application, but were only soaked with the solution so that there was passive transport of the substance through the membrane. The results showed a correlation of 0.99 between the application to the skin and the concentration applied to the skin, with a superiority of the latter in the group that received iontophoresis application compared to the group that was only exposed to glibenclamide.

Iontophoresis is used with other substances to evaluate a possible increase in blood perfusion (36). Agarwal et al. (70) showed that iontophoretic application of acetylcholine in ten healthy volunteers increases blood perfusion. In another study, Kigasawa et al. (71) studied the effectiveness of iontophoresis with the use of ribonucleic acid (small interference RNA) in a mouse model for atopic dermatitis (endogenous eczema). The cathodic application was 0.3 mA/cm^2 for one hour. The distinguishing factor of the study was application of RNA restricted to the epidermis (target site) without going into the dermis, thereby demonstrating the effectiveness of therapy for atopic dermatitis.

Prasad et al. (72) evaluated the use of iontophoresis with methotrexate (folic acid antagonist) used for treatment of cancer, psoriasis and rheumatoid arthritis, also in rats. The application intensity was 0.2 mA/cm^2 for one hour in excised abdominal tissue. The results showed that the tissues with application of iontophoresis had a 32% increase in the concentration of methotrexate as compared with the group that had only passive drug application.

Conclusions

Iontophoresis is a means of applying pharmaceuticals to the organism based on physicochemical principles of attraction or repulsion of charges. The material consulted in this study allowed the understanding of how this technique has been employed for diagnostic and therapeutic procedures. Given the advantages observed in the use of iontophoresis such as transdermal topical application, its clinical and rehabilitative use is recommended. However, similar to other therapeutic modalities, its use should be preceded by a proper study of its possibilities and limitations. With research and development of new technologies, such as pharmaceuticals applied with microcapsules, the use of iontophoresis is more precise and controlled, increasing its treatment effectiveness. Currently the use in the field of physical therapy has a practical application and good results, especially since it is noninvasive and enables topical application of pharmaceuticals.

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