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The Challenge in Combining Pelotherapy and Electrotherapy (Iontophoresis) in One Single Therapeutic Modality

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Abstract: Pelotherapy and electrotherapy are therapeutic methodologies with proven success in physical medicine and rehabilitation (PMR) and dermatology fields. The main purpose of these therapeutic modalities is to reduce pain, accelerate wound healing, alleviate muscle spasms, and improve mobility, and muscle tone. Their main challenge is in the passage of some ionic species through the skin barrier. The use of drugs, such as diclofenac, corticosteroids or steroids, has gained widespread efficacy recognition in physical therapy and the therapeutic action of these drugs is widely studied in experimental and clinical trials. Unlike pharmaceutical and cosmetic clays, peloids are not subject to any prior quality control or subject to any specific European regulation. The dermal absorption values are an integral part of the risk assessment process for peloids. This work explores the converging points between these two transdermal drug delivery systems (TDDS) and the presentation of methodologies to achieve peloid safety compliance, especially concerning the potential and degree of toxicity arising from ion exchange and trace elements. TDDS is applied to the pharmaceuticals industry and drug is the generic term for the active substances released into skin tissues. The transdermal delivery of drugs or clay components with therapeutic properties is limited due to the excellent barrier function of the stratum corneum. The transdermal drug delivery of pelotherapy is enhanced by temperature and electrically by iontophoresis. The low voltage of iontophoresis and sweat phenomena with pore dilation driven by pelotherapy allows the use of the same pathways: hair follicles and sweat pore. The therapeutic integration of iontophoresis and pelotherapy focused on patient benefits and low safety-related risk may contribute to the outstanding physiological performance of pelotherapy, specifically, in the way the essential elements and exchange cations pass through the skin barrier. The validation of an innovative iontophoretic systems applied to pelotherapy can also promote future challenges in the obtaining of the ideal therapeutic control of peloids and the clinical validation of results with physiological efficacy recognition.

Keywords: thermalism; pelotherapy; transdermal drug delivery; electrotherapy; medical geology

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1. Introduction

Balneotherapy protocols applied in rehabilitation medicine maintain some conservatism regarding classical practices, based on the experience of bathing, mineral–medicinal water intake, mud baths or mud cataplasm application, physical activity, and dietary discipline [1]. Nevertheless, some of those protocols started to introduce other therapeutic modalities, conceived in the context of thermalism and medical hydrology. The growing increase of health tourism in Europe, the abundance of resorts associated with wellbeing, the building rehabilitation of historic thermal spa/medical hydrology centers (in certain cases using thermal water also for heating buildings) and the increased demand in the natural cosmetics market, have contributed to the popularity of classic thermal treatments and opened doorways for new therapies and new products (Figure 1).

Figure 1. Mud baths (Poça da Dona Beija, S. Miguel, Azores, Portugal).

The application of peloids at the end of the last century was quite common in some Portuguese thermal centers, where natural and artificial peloids were used for the treatment of rheumatic and musculoskeletal diseases or eczematous dermatoses, namely psoriasis [2].

The World Health Organization (WHO) has promoted the valuation of traditional medicine, also called unconventional medicine, as an important part of health services in the prevention and treatment of chronic diseases and is gaining acceptance in the scientific community. WHO has updated its strategy for traditional medicine: 2014–2023 [3] to support health authorities in finding solutions that provide greater focus on patients' health. The main objectives of the strategy are to support Member States in traditional and complementary medicine (TCM) in people-centered health and wellbeing and to promote the safe and effective use of TCM by regulating products, practices, and professionals. The guidelines include the development of national policies formulated and supported by existing knowledge, the strengthening of safety, quality, and effectiveness through regulation, and in an inclusive perspective, to integrate TCM services into national health systems.

WHO supports its strategies for balneology or medical hydrology through the supervision of studies carried out by the World Hydrotherapy Federation (FEMTEC) and the Italian Foundation for Research on Thermal Therapy (FoRST). The FEMTEC and FoRST joint project, Hydroglobe, highlights the efficacy of medical hydrology, based on solid scientific evidence and worldwide research, referring to this type of treatments as a broader concept of health.

Thermal or spa therapy, as reported by several authors, addresses a broad spectrum of therapeutic modalities, including hydrotherapy, balneotherapy, physiotherapy, pelotherapy and exercise. These therapeutic modalities have been used in medicine as support in the prevention, treatment, and rehabilitation for several health infirmities, having success in

numerous European countries, Japan and Israel. Nevertheless, the clinical practice differs from country to country.

The goal of thermal therapies is in pain-reduction, muscle spasms relief, muscle strength improvement and functional mobility. These treatments continue to be discussed, as well as their role in medicine, hampered by the lack of knowledge of the action mechanisms of thermal baths and mud cataplasms and the problematic distinction between the effects of thermal applications and the benefits that may derive from being in a spa or thermal environment [4,5].

Studies developed in bathing and thalassotherapy centers for the application of therapeutic muds, such as thermotherapeutic technique, have shown the best results in skin and musculoskeletal disorders [6].

According to Gomes et al. (2013), pelotherapy consists of the topical use of a peloid for therapeutic or cosmetic purposes, and the application of a medical peloid should be administered by medical prescription and supervision of health and medical centers. The authors also consider, that when clay maturation occurs in the natural environment, the resulting peloid is called a natural peloid and can be considered a curative mud and in other cases, it is designated simply as a peloid. Additionally, considering their composition peloids, may be classified as inorganic peloids, organic peloids and a mixture of peloids, also being able to be designated of medical peloids or cosmetics according to their application [7].

We take the current European regulatory and legal framework on cosmetic products, EC No. 1223/2009, to be the nearest compliance guideline for the quality criteria established for peloids or clayey products. According to this Regulation on cosmetic products, a cosmetic product is defined as "any substance or mixture intended to be placed in contact with the external parts of the human body with the main, or exclusive aim, of cleansing or perfuming it, changing their appearance or smell, as well as protecting and maintaining it". The safety evaluation of cosmetics in relation to its chemical content is regulated by the provisions of EC No. 1223/2009, the EU REACH Regulation (EC No. 1907/2006), Commission Regulation on claims in cosmetics products (EU No. 655/2013) and by national laws, where cosmetics products will be marketed. However, it is unclear whether some products are cosmetic under the definition in the cosmetic regulation or whether they fall under other sectorial legislation.

The European legal framework governing medicinal products for human use, defines medicinal products as "any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis". Peloids are promoted in many European Thermal Resorts as therapeutic clays. It is unclear if they fulfill the criteria for definition as medicinal products while their medicinal properties are emphasized. Peloids may fall be defined as borderline product, having combined characteristics of medicinal products along with cosmetics.

Physical therapy and physical medicine are fields of medicine that use specific methods in rehabilitation, therapy and prevention of numerous diseases, and the continuation of outpatient and hospital treatments of chronic diseases that require rehabilitation treatments [8]. As in naturotherapy, which represents a diversity of natural therapeutic methodologies, the same happens in electrotherapy in that it is often considered by therapists as a set of therapies, in which electric currents, ultrasound or laser are used. The rehabilitation concept in the discipline of physical medicine has its origin in the 1960's and coincides with the official recognition of Physical Medicine and Rehabilitation (PMR) as an independent medical specialty [9].

This medical specialty is defined in the PMR section of the European Union of Medical Specialists as "an autonomous medical specialty whose purpose is to promote physical and cognitive functionality, activity (including behavior), participation (including quality of life)

and the modification of personal and environmental factors. Therefore, it is responsible for the prevention, diagnosis, treatment and organization of the rehabilitation of individuals with incapacitating medical conditions and co-morbidities in all age groups".

The main goal of thermal therapy is to reduce pain, relieve muscle spasms and improve mobility and muscle tone [4], such as electrotherapy, the most widely used therapeutic modality in PMR. Physiotherapists use iontophoresis as a treatment modality with the purpose of avoiding the systemic circulation of the patient. It is presented as a way of supporting the treatment of several clinical conditions, namely, treatment of inflammation, pain relief, local anesthesia, treatment of soft tissue mineralization, wound and infection treatment, among others.

Iontophoresis is a technique of transdermal drug delivery and is considered to have numerous theoretical advantages when compared to other forms of drug delivery. The main advantage is the fact of being a non-invasive technique that increases the permeability the of skin to ionically charged substances, improving the therapeutic efficacy, avoiding metabolism, and preventing the inconvenience caused by parenteral administration as well as oral administration of drugs, responsible for the absorption by the systemic circulation, reducing the possibility of dosage variation [10,11]. The possibility of "programming" the administration of the ionically charged substances provides a therapeutic framework that enhances patient compliance.

Pelotherapy is also a non-invasive technique, however passive, for the application of muds for therapeutic purposes, despite the therapeutic characteristics being empirical because there are no criteria established for the certification of clay products with therapeutic action [12].

The skin route for peloids' local therapeutic action or for peloids' systemic action, provides two routes of penetration, via the pores, sweat glands, sebaceous glands, and hair follicles and via diffusion through the stratum corneum.

Considering the general view of pelotherapy, associated with thermalism and electrotherapy (iontophoresis) with physical medicine and rehabilitation, the transdermal delivery of drugs (e.g., diclofenac, corticosteroids or steroids) or clays with therapeutic properties is limited due to the excellent barrier function of the stratum corneum. The main objective of this type of transfer systems is to obtain optimum therapeutic control, which results in strong patient benefits and low safety-related risk, especially regarding the potential and degree of toxicity arising from ion exchange.

In physical rehabilitation, the treatment of patients with pain associated with rheumatic disorders gets excellent relevance, using the afore-mentioned action mechanisms that can contribute to the treatment and relief of pain and improvement of the functional performance of the joints. In this context, electrotherapy (iontophoresis) and pelotherapy can be included as treatments for pain relief and improvement of motor functionalities: electrotherapy, by transcutaneous electrical nerve stimulation (TENS) with transdermal drug passage, and pelotherapy by heat therapy and transdermal passage of essential elements of peloids.

Since the challenge for pelotherapy and electrotherapy (iontophoresis), as therapeutic methods, is in the passage of some ionic specimens, the study of the use of iontophoresis in therapeutic peloids is considered relevant, involving the application of an electric potential (voltage) between the peloid and the skin, accelerating the transfer of the clay ions and conferring on this method utility in the transfer efficiency of essential elements of the clay while analgesic, antiseptic or anti-inflammatory agent (Table 1).

Table 1. Identification of convergence points between the two therapeutic modalities.

	Pelotherapy	Electrotherapy (Iontophoresis)
1. Health Area	Medical Hydrology	Physical Medicine and Rehabilitation
2.Treatment vehicle	Skin	Skin
3.Type of treatment	Noninvasive	Noninvasive
4.Therapeutic substance	Medicinal or cosmetic peloid	Drugs or cosmetics
5.Transdermal delivery	Passive	Active
6. Energy source	Heat	TENS [1]
7. Localized physiological phenomena	Vasodilation Local hyperemia Local analgesia	Vasodilation Local hyperemia Local analgesia
8. Average reference treatment time	20–45 min	20–45 min
9. Most common treatments	Rheumatism Musculoskeletal pain syndromes Dermatosis	Rheumatism Musculoskeletal pain syndromes Dermatosis
10. Local and systemic effect	Anti-inflammatory Increased muscle tone Analgesic Wound healing	Anti-inflammatory Increased muscle tone Analgesic Wound healing
11. Scientific reports	Empirical evidence	Experimental evidence

[1] Transcutaneous electrical nerve stimulation.

The next sections will detail the health and wellbeing significance of pelotherapy and electrotherapy, the skin's role in effective topical applications of medicines or other substances, transdermal drug delivery, as an innovative method, for delivering therapeutic or aesthetic substances, and the main inhibitors and promotors of a good dermal permeation. Section 4 will present the importance of pelotherapy and electrotherapy in the physical rehabilitation field.

2. Therapeutic Methodologies

2.1. Pelotherapy

Since ancient times, mankind has empirically used clays, muds, or clay soils for therapeutic purposes, through ingestion or topical application in the form of poultices or mud baths. The physicochemical properties of clay minerals can be fundamental in maintaining health, but in certain circumstances, their excess or deficiency can be a factor that potentiates diseases [13]. Several authors have characterized the main mineralogical and chemical components of clays and compared them with the desired composition of peloids usually used in pelotherapy [7,12–15].

Clays are distinguished by their geological formation (residual and sedimentary) and their complexity and variability are due to the quantitative and qualitative variation of the clay and non-clay minerals (such as quartz, feldspars, and other accessory minerals) forming them, to the variation in the dimensional distribution of the mineral particles (namely the actual content of clay fraction) and to their textural characteristics.

Clays are used in pharmaceutical formulations, spas and aesthetic medicine as active ingredients or excipients. When introduced into the formulations as excipients they allow the organoleptic characteristics of the formulation to improve, such as taste, smell, color, or the physical-chemical properties (e.g., viscosity). They can also be an adjunct to make the preparation of the formulation easier and can promote the disintegration of the formulation

when administered orally. Clay's therapeutic action, as an active ingredient, is used in pharmaceutical formulations administered orally (e.g., gastrointestinal protectors, laxatives, antidiarrheals) or topical applications (e.g., dermal protectors and cosmetic). Its use in spas is related to the therapeutic activity of clay minerals and in aesthetic medicine, in cleaning the skin and combating lipodystrophies, acne and cellulite [14].

The pharmaceutical and cosmetic industry uses clays in their formulations, being subject to prior control before being used. Clays are used in pharmaceutical products, as excipients or as active substances, due to their high retention capacity, colloidal and expansive properties, useful for modulating the release of drugs in the body [14], chemical inertia and low or no toxicity to the patient [15].

The clay minerals used in pharmaceutical formulations are smectite [$(Na,Ca)_{0.33}(Al,Mg)_2(Si_4O_{10})(OH)_2 \cdot nH_2O$], palygorskite [$(Mg,Al)_2 Si_4O_2 10(OH) \cdot 4H_2O$], kaolinite [$Al_2Si_2O_5(OH)_4$] and talc [$Mg_3Si_4O_{10}(OH)_2$] [15]. The clay-drug interactions presented in most studies refer to the application of natural clays or synthetic and semi-synthetic derivatives to perform specific functions in new drug delivery systems, aimed to increase the stability of the drug and change the transmission pattern using clay minerals [14].

The use of kaolinite, talc and smectite in dermatological protectors is based on its absorbing capacity of skin's secretions, adhering to the skin and forming a film that mechanically protects it against external physical and chemical agents, resulting in a refreshing action by creating a large surface for its evaporation, and promoting an antiseptic action as it creates a low humidity surface for the development of bacteria. Palygorskite is not used in dermatological protectors due to some doubts regarding the carcinogenic effect if inhaled. In cosmetics, clays are recommended for inflammatory processes (e.g., boils, acne, ulcers) used in the form of creams, powders, emulsions, with talc and palygorskite being recommended only for liquid preparations [15].

Peloid, from the Greek pelòs, was proposed by Judd Lewis, in 1933 and was definitively adopted by the International Society of Medical Hydrology in 1949 at the IV International Scientific Conference of Dax [7].

The most recent concept of peloid is defined by Gomes et al. (2013), and is designated as products formed by the spontaneous or artificial blending of natural mineral water, seawater or salt lake, with a solid component (organic or inorganic), resulting from geological or biological processes (or both) which, in the natural state or after preparation, are used topically for therapeutic purposes in the form of poultices or baths. In addition, the use of organic compounds has been shown to be associated with the biological metabolic activity [6].

The classification of therapeutic clays is usually made by the characteristics which distinguish them, namely by their composition, preparation, and use. Most studies associated with the use and effect of peloids are based on three criteria [16], (i) technical (preparation practices), (ii) physicochemical (intrinsic properties or composition) and (iii) clinical-biological (preponderant biological and therapeutic action).

The International Society of Medical Hydrology has characterized some peloids, according to their solid component (inorganic or mineral), organic components and depending on the chemical nature of the liquid component [2].

In the formulation of thermal muds, the maturation time of the mixture of the liquid and solid phases, sun exposure, agitation of the mixture, temperature and the properties of its components are decisive in the characterization of the peloid [12].

Unlike pharmaceutical and cosmetic clays, peloids are not subject to any prior quality control or subject to any specific European regulation, as is the case of mineral waters for human consumption (Council Directive 98/83/EC of 3 November 1998).

Regulation (EC) No. 1223/2009 of the European Parliament and of the Council of 30 November 2009, concerning cosmetic products, states that "this regulation relates only to cosmetic products and not to medicinal products, medical devices or biocidal products", considering that the "delimitation follows in particular from the detailed definition of cosmetic products, which refers both to their areas of application and to the purposes of

their use". On the other hand, it states that to assess "whether a product is a cosmetic product has to be made on the basis of case-by-case assessment, taking into account all characteristics of the product".

Directive 2001/83/EC of the European Parliament and of the Council, of 6 November 2001, defines "Medicinal product: Any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting, or modifying physiological functions in human beings is likewise considered a medicinal product."

The peloids used in thermal centers and spas are diverse, resulting from the mixture of clay minerals with salt water (sea or lake) or medicinal-mineral water (maturation process) or resulting from the mixture of clays with paraffin ("paramuds"). However, nowadays, because of the regulation and safety compliance, there is increasing use of artificial peloids, where raw materials are controlled and engineered to be placed on the market accordingly the legislation.

As for the application techniques, they are characterized in two types: (i) general if the peloid is applied to the whole body, and (ii) local if only covers some of the body joints. Heat promotes skin vasodilation, hyperemia, perspiration and pore dilation, and improves the assimilation and penetration of the peloid's essential elements into tissues [17]. Concerning the peloid's temperature, in dermatological treatments, it is applied, in a thin layer, at temperatures between 36 °C and 37 °C and in rheumatic or musculoskeletal treatments, direct application to the skin at temperatures between 44 °C and 45 °C is considered [18].

Medical interest in using pelotherapy for the treatment of dermatological and musculoskeletal chronic conditions is typically based on the fact that it is a treatment option with minimal side effects. However, hot peloids are contraindicated when the skin has an acute inflammatory process.

Peloids simultaneously fulfil the definition of cosmetic product and medicinal product. However, they cannot be classified simultaneously as cosmetic products and medicinal products, given the exclusivity scope of the Directives that regulate them. These types of products are called "borderline products" and should be evaluated by the most demanding legislation and on a case-by-case basis, that is, according to the legislation applicable to medicinal products.

2.2. Electrotherapy

Electrotherapy is applied for several physiological effects, namely pain relief, muscle work and relaxation, stimulation of tissue flows, tissue regeneration and transdermal medicinal products (drugs) application. The most used current for this therapeutic purpose is the transcutaneous electrical nerve stimulation, TENS. The nature of these currents allows the reduction of skin impedance and the stimulation of the transport of ionic substances, for very low current values, in the order of mA units (below 5 mA), being, therefore, a safe and painless process.

Pain can be clinically present in several ways and associated with multiple symptoms and can be characterized as acute (symptomatic) and chronic (pathological). Acute pain is usually the result of an injury, while chronic pain has no biological function and remains even after healing, being itself considered a disease.

Each physiotherapy technique has a neurophysiological explanation with its own mechanisms of action. The inhibitory modulation of pain occurs with the reduction of peripheral and central stimuli that sensitize the nervous system [19].

In 1965, Ronald Melzack and Patrick Wall published the first interpretation of the pain phenomenon with the designation of "Gate-control theory of pain". This theory was based on physiology and associated with sensory aspects and psychological aspects of pain perception. The theory of the pain gate introduced the concept of the experience of pain as not being the result of a linear process that begins with the stimulation of pain transmission routes to the peripheral nervous system and ends with the experience of pain in the central

nervous system. What really happens is that the nerve impulses that potentiate the pain signal in the peripheral nervous system, are subject to a few modulations in the spinal cord before the pain experience is transmitted to the central nervous system. According to the authors, the gate mechanism is modulated by emotions, cognitive state, and past experiences. A painful stimulus is detected by pain receptors, called nociceptors, which can be of three types: thermal, mechanical and polymodal (simultaneous detection of mechanical and thermal stimulation). The nociceptive fibers, conducting the stimulus to the central nervous system, more specifically to the spinal cord, can be Aδ (fast response) or C (slow response). From the spinal cord, it goes to the brainstem, thalamus and finally the cerebral cortex where pain perception is triggered [20].

Another theory, the endogenous opioids system, is associated with the fact that the nervous system has several receptors for opioid substances, beta-endorphin, dynorphins and met- and leu- enkephalins [21]. Electrical stimulation can lead to the release of endogenous opioid substances and decrease the sensation of pain. The release of opioids is also used to explain the action of low-frequency TENS (2 to 5 Hz) [22].

Iontophoresis is a non-invasive electrotherapy method, quite common in physical medicine and rehabilitation, for transdermal transmission of drugs, based on the transfer of charged molecules, using low-intensity electric current.

The advantages of its use refer to the faster release of the drug into the skin, the passage of macromolecules and better control of the dose to be administered. Inverse iontophoresis has also been studied to allow the extraction of molecules from the skin, having been applied in glucose monitoring studies [23].

It is also a technique with potential in the diagnosis and monitoring [24] of a noninvasive form of clinically important molecules in the human body [25].

Iontophoresis occurs by the application of an electric field, creating a potential difference between two electrodes, one with positive polarity (anode) and the other with negative polarity (cathode). These electrodes are placed in a certain position that prevents current from passing through the cardiothoracic box. The maximum limit of the current applied before the patient manifests physical discomfort is 0.5 mA/cm^2. The combined use of iontophoresis and electroporation has been shown to be more effective in passing peptides, proteins, genes and oligonucleotides [25], expanding the scope of transdermal transmission to larger molecules by the improvement of the transport, the fast passage of large doses, better modulation control or transmission programming [26].

As the electrical current travels through the body, the cations present at the anode move towards the cathode, while the anions present at the cathode move in the opposite direction. By placing electrolytic solutions on the electrode of the same ionic nature, with the desired drug, its transdermic introduction is achieved. Negatively charged drug molecules are repelled by the cathode while positively charged ones are repelled by the anode. Electro-osmosis or electromigration represents the amount of flow that passes into the bloodstream, depending on the physicochemical properties of the molecules and the polarity of the applied current.

Transdermal drug delivery by iontophoresis has been widely accepted in PMR for localized therapies, being frequently used in the localized application of analgesics and anti-inflammatory drugs and in the treatment of hyperhidrosis. This non-invasive method has been widely used for local anesthesia in pediatric patients, allowing for rapid and effective anesthesia before medical procedures such as intravenous injections or blood collection [25,27].

Studies carried out to assess the initial electrical resistance and overtime of commercial gels in physiotherapy and liquids used in electrotherapy for the electrode-skin interface, concluded that gels, drinking water and saline solutions are the most suitable for therapeutic electrical stimulation because they maintain low resistance during skin stimulation, in contrast to the use of distilled or deionized water with high resistance to the passage of electric current [28].

Some factors condition the iontophoretic effect. The pH of the solution is very important because it determines the ionization of the compound. The pH of the solution will have to be well determined and controlled to ensure that the drug is ionized and that it preserves the integrity of the skin [23]; this is due to the variation in the degree of ionization and the selective permeability of the skin [25].

The size of the molecule and ionic strength [25] are also decisive when passing through the stratum corneum. In general, small, and hydrophilic molecules are transferred more quickly than the largest and lipophilic ones, with some exceptions such as the case of peptides [23].

The integrity of the skin surface, namely the thickness of the stratum corneum, the presence or absence of hair, wounds, skin diseases (e.g., atopic dermatitis or psoriasis), the hydration status of the skin surface, also interfere. Parameters that can be adjusted by the operator and modify the iontophoretic transfer are the method of applying the current (continuous or pulsed) [25] and the amount of current, the area of the skin section in contact with the electrode and the concentration of the substance or drug because there is a quasi-linear relationship between concentration and flow. Saturation of iontophoretic transport may occur when the flow reaches the maximum concentration limit [23].

The known side effects resulting from the use of iontophoresis are, in most cases, adverse reactions with a very small dimension, being well tolerated by patients. The reactions that occur most frequently are associated with hypersensitivity to electrical stimulation, with pruritus, erythema, and irritation of the skin surface where iontophoresis was applied or sensitivity to the medication administered. This type of adverse reactions increases the risk of occurrence if the exposure time and/or the current value is increased. If the current density through the skin pores is greater than the current per unit area applied and depending on the density of the pores in that area, the possibility of skin injuries induced by the current may increase [23].

This method is contraindicated for patients with recent scars, metallic prostheses, pacemakers or any other type of implanted electronic device, pregnancy, heart disease/dysrhythmias, epilepsy, cancer, dermatological conditions in the region of application, inflammatory processes, fever, changes in skin sensitivity, direct application in the cardiac area and abdominal application in individuals with peptic ulcer [29].

3. The Skin's Role

The skin is the largest organ in the body, which covers an area of about 1.80 m^2, with a thickness of 2.97 $\pm$ 0.28 mm and its main function is to protect the body from undesirable effects of the environment. The main characteristics of the skin are elasticity, strength, self-healing, and receiving one-third of the total blood circulation [30]. The isoelectric point of human skin is between 4–4.5, which is below its pH under normal conditions [23]. The skin protects from heat, light, injuries, and infections. Although the main role is protective, it also regulates body temperature, prevents water loss, and inhibits the entry of bacteria [11].

The skin consists of three different layers: epidermis, dermis, and hypodermis. The outer layer of the epidermis is formed by the stratum corneum (s.c.) and due to its high density and low hydration, it acts as a skin barrier. The dermis is the middle layer, located between the epidermis and subcutaneous tissues, being the thinnest layer of the skin. The dermis is a vascular network responsible for skin nutrition, repair, regulation, and immune response. The subcutaneous layer, the hypodermis, is the deepest layer, after the dermis and is mainly made up of fat. The hypodermis acts as a heat insulator, shock absorber and energy storage.

Transdermal drug delivery requires considerable development in the field of research. The design needs for a topical compound requires primarily the interaction knowledge of what happens between the formulation and the skin [11,31]. The topical drug delivery system is specially designed to pass active therapeutic substances through the skin. Since the skin is considered a multifunctional organ, it has a limitation of being less permeable when

passing through the stratum corneum, constituting an effective barrier to the passage of substances, and several vehicle systems that surpass this barrier have been developed [11].

The stratum corneum is about 10–20 µm thick and is composed of intercellular lipids and dead cells, the corneocytes, preventing the passage of macromolecules, so it is usually necessary to find improvement strategies for passive penetration (use of supersaturated and penetration enhance solutions) and physical (electroporation and iontophoresis) to overcome the barrier [32].

The methods for drug delivery and the processes for administering pharmaceutical compounds have been used to obtain therapeutic effects in both humans and animals. The transdermal drug delivery means the passage of a substance or drug through the skin in the form of a plaster, cream or lotion that passes through the skin and enters the bloodstream. This process depends on some factors, such as the nature of the skin barrier, the balance between the physicochemical properties of the membrane and the drug, application time, skin location, skin conditions, the vehicle's effect on the stratum corneum, properties and type of formulations and the available technologies, which facilitate transdermal transport [10].

The properties of the skin have an important role in the topical application of medicines or other substances. Pharmacokinetic studies, including in vivo microdialysis experiments with volunteers, have shown that vasodilation improves the system of assimilation and penetration of substances into tissues, while vasoconstriction has the opposite effect, causing accumulation in tissues. The compounds only reach the systemic circulation of the skin after being absorbed by the stratum corneum [31].

In an effective transdermal drug delivery system, the drug must infiltrate the skin tissues and go directly into the bloodstream without accumulating in the skin layers. The temperature of the skin and the blood flow allow the rate of penetration of the substance to be demonstrated by the relationship between the increase in the permeability of the skin and the increase in its temperature increase, caused by the thermal energy necessary for diffusion, the solubility of the drug in the skin tissues and the increase in skin vasodilation [10,30].

According to Dancik et al. (2014), some factors affect the physiology and structure of the skin, influencing systemic cutaneous assimilation and the impact of the administered substance, namely the person's age, the health status of the skin, the dosage of the substance, administration procedures of the substance and environmental conditions [31].

Skin hydration plays an important role in dermal absorption, decreasing with age, as well as enzyme activity and blood circulation in the skin. Low blood circulation in older people suggests that drug release is slower, which has a negative impact on the drug flow gradient [30].

To optimize the penetration of different drug molecules through the skin, topically and transdermally, different methods are used, such as drug-vehicle interactions, use of vesicular transporters, nanoparticles, modification of the stratum corneum and methods of conducting energy [11]. The drug absorbed after transdermal application can be detected by measuring its levels in the blood, in the excretion by urine and its metabolites and by the clinical response of patients [10].

Most of the toxicology studies carried out in the context of cosmetics, therapeutic products and industrial solvents involving skin exposure rarely incorporate information on the skin's permeability kinetics. Currently, pharmacokinetic models based on the physiology and structure of the skin are the most efficient way to incorporate a variety of parameters intrinsic to the skin and dependent on extrinsic factors associated with exposure. Physiological–pharmacokinetic models allow the integration of data availability in vivo, in vitro and in silico, to quantitatively predict the kinetics of assimilation at the site of interest. Considering what is required in the current regulation, it becomes an essential factor in risk assessment [31].

3.1. Transdermal Drug Delivery (TDD)

Transdermal drug delivery is considered an effective and innovative method for delivering substances through the skin. The process consists of the passage of a substance through the skin, passing through the tissues and into the blood circulation. The passage of therapeutic quantities of substances or drugs through the skin and into blood circulation allows obtaining speed in its effects. However, the skin is still a barrier. Most of the research work carried out focuses on the ease with which drugs or other substances can pass through the skin and in controlled concentrations. TDD has become a viable and market valued drug delivery method, allowing the administration of controlled doses and with demonstrated clinical benefits, and is probably the safest form of controlled drug delivery [10].

The topical application of therapeutic substances facilitates the patient's adherence to the treatment because it is easy to apply and remove. It avoids the risks associated with intravenous therapies and eliminates any variables that the treatment depends on, such as gastrointestinal absorption, mobility and intestinal transit or empty stomach [11].

Topically applied drugs have an absorption sequence: first, the drug is released by TDD, absorbed by the first skin barrier, the stratum corneum, then the epidermis and dermis to the bloodstream and transported to the site where it is expected to have a therapeutic effect [10].

The term TDD is used for all therapeutic formulations that are administered topically and whose transmission is done through the skin until the systemic circulation. There are numerous plasters of various types and sizes on the market for the treatment and prevention of systemic diseases, mostly of a medicinal nature.

The drugs administered topically through the skin fall into two categories of application: (i) local action, through skin application and (ii) exerting action on the stratum corneum or systemic, modulating the function of the epidermis and/or dermis [33].

Topical application systems allow a controlled action on the drug dose in plasma, thus reducing the possibility of overdosing or low dosage. It also allows a reduction in the substance frequency administration. On the other hand, if intolerance or toxicity reactions occur, treatment is easily finished [11], which is why its effectiveness and safety must be supported by in vitro and in vivo trials.

Despite TDD limitations regarding skin permeability, age, application spot and skin diseases, the advantages are notorious when compared with other forms of drug administration, as following [10]:

- The skin represents a relatively large and accessible surface for absorption and prevention of overdose or unwanted effects;
- Reduces gastric adverse drug reactions (ADRs) and increases tolerance;
- First-pass metabolism of the drug is prevented (liver metabolism);
- Reduces pharmacokinetic peaks and troughs, for example, peak drug concentration in plasma;
- Suitable for drugs with a short life cycle, high lipophilicity, and narrow therapeutic index drug;
- Increased performance time;
- Easy to apply and remove in case of toxicity;
- Drug absorption is not affected by pH, enzyme activity and interactions between the drug and food;
- Reduced dose or frequency of administration and increased patient adherence;
- Improves drug stability and solubility, reducing response delay and increasing transmission rate.

The passage through the different layers of the skin until it reaches the systemic circulation, can occur through the trans-epidermal route (transcellular and intercellular), through the sweat glands and through the hair follicles [25,30,34].

3.2. Dermal Permeation Promotors and Inhibitors

The use of physical methods to promote skin permeation is achieved by heat in pelotherapy and by the application of low intensity electric current in iontophoresis. In the case of drugs, the increase in permeation can be achieved by mechanisms such as electro-osmosis (solutions without charge), electrorepulsion (solutions with charge) or electro-disturbance, for both cases. The substances transport through the skin first occurs via pores and heat is a transdermal enhancer for pore dilation.

Microdermabrasion is another physical method used to promote the permeation of drugs through the skin, which can selectively remove the full thickness of stratum corneum (s.c.), with low damage to deeper tissues and increase skin permeability. These kinds of treatments are commonly used in the aesthetic field for the treatment of acne, scars and other dermocosmetics therapies. In pelotherapy, it can be enhanced by using peloids with high abrasive index [35], which gently sand away the thick outer layer of the skin, safely.

The pH is an important variable in pelotherapy. Peloid pH is important for the therapeutic protocol definition and must be physiologically tolerated [36]. On the other hand, pH is a critical variable in iontophoresis because it affects skin charge and electroosmotic flow [37].

4. Health

According to the European Agency for Safety and Health at Work, musculoskeletal injuries are one of the most common work-related illnesses, affecting millions of European workers, at a cost of billions of euros. They consist of injury or disturbance of the joints or other tissues, normally affecting the dorsal-lumbar region, the cervical area, the shoulders, and the upper limbs.

Rheumatic diseases, defined by the functional changes in the musculoskeletal system, resulting of a non-traumatic cause, which can be acute, recurrent, or chronic and affect any age group are the most common group of diseases in developed countries and represent an important medical, social, and economic problem, having also a significant negative impact on public health concerns.

Osteoarthritis (OA) is a chronic systemic disease that affects the joints, tendons, muscle, connective, and fibrous tissues, being a prevalent locomotor disability worldwide. A few clinical studies tested the effectiveness of thermal therapy in patients with OA [38–41]. Osteoarthritis Research Society International (OARSI) guidelines for the non-surgical management of knee osteoarthritis considered Balneotherapy appropriate for individuals with multiple-joint OA and relevant co-morbidities despite the uncertainty for individuals without relevant co-morbidities or with knee-only OA [42]. Only the clinical trials for pain relief using baths containing thermal mineral waters were considered.

4.1. Physical Rehabilitation with Pelotherapy

As previously mentioned, pelotherapy consists of the local or generalized application of thermal mud, the peloids. The therapeutic interest of peloids, in the natural state or after maturation, is due to the use of the thermal effect (“Unspecific effects”), with temperatures that in general baths range from 37 °C to 38 °C and in poultices up to 45 °C, as well as “crenotherapeutic” effects, depending on their physical–chemical composition (“Specific effects”) [2].

Teixeira F., 2011, states that the choice of silica and sulfur-rich peloids for treatments in dermatology, cosmetics and complementary therapies for rheumatic and musculoskeletal diseases are advantageous due to their scaling actions (silica and sulfur), buffering (colloidal silica), antiseptic (sulfur) and anti-inflammatory (sulfuric waters) actions.

Heat, from 47 °C to 50 °C, plays a fundamental role in the beneficial effects of pelotherapy since it reduces muscle contraction and provides relaxation associated with pain relief [43] Therapeutic action through the effect of heat provides numerous reactions, such as vasodilation, sweating, cardiac and respiratory stimulation, and may be related to

anti-inflammatory therapeutic effect or the cationic exchange between the mud and the skin [2,12].

In scientific literature, several studies have contributed to support the beneficial effects of peloids in treating pain, improving functional capacity and quality of life. The mechanism by which immersion in thermal water or the application of mud cataplasms relieves pain in rheumatic patients is not yet fully understood. The distinction can be made between common, non-specific mechanisms (hydrotherapeutic) and simple baths in warm and specific water (hydromineral and crenotherapeutic) that depends on the physical and chemical properties of the water used, the latter being difficult to identify and evaluate. Within the scope of pelotherapy, clinical studies have been carried out to assess the therapeutic effect of the use of clays in patients with rheumatic and musculoskeletal disorders. Most of these studies compare clinical results considering parameters such as the perception of pain, functional capacity, the severity of the disease and medicine intake [43].

Some biochemical evidence relates pelotherapy to increased plasma on β-endorphin levels and secretions of corticotropin, cortisol, growth hormone and prolactin. Recent studies have shown that pelotherapy induces a reduction in circulating levels of prostaglandin E2 (PGE2), leukotrienes B4 (LTB4), interleukin-1β (IL-1β) and the tumor necrosis factor-α (TNF-α), important mediators of inflammation and pain [4]. Other studies also demonstrate that pelotherapy decreases inflammatory index and has a positive effect on antioxidant status markers and increased type 1 insulin growth factor [6,44].

Some of these scientific studies have shown changes in the mechanisms of enzymatic and molecular action after the application of pelotherapy. They have also shown results in chondrocyte metabolism, producing a protective effect on joint cartilages after a pelotherapy treatment cycle, as well as influencing antioxidant reactions, inhibiting free radicals. Numerous studies relate the effectiveness of using pelotherapy for knee osteoarthritis and fibromyalgia by improving pain perception, functional capacity, or quality of life. Some of these studies compare pelotherapy with pharmacological treatments and physical rehabilitation techniques, showing greater efficacy in pelotherapy [43,45].

A clinical study carried out with 24 patients with spondylosis associated with inflammatory bowel diseases (Crohn's disease and ulcerative colitis), over a period of two weeks, showed a reduction in the biochemical indices associated with spondylosis, at the end of a cycle of 12 mud treatments and 12 thermal baths. In the clinical study, 12 of the patients were taken as control, which led to the conclusion that patients with spondylosis associated with inflammatory bowel diseases are well tolerated and could be useful as a complementary treatment to drug therapy in patients with inflammatory bowel diseases [46], where oral drug tolerance is very low. The use of thermal muds in the treatment of osteoarthrosis allowed, in some studies, a correlation between the therapeutic effects and the existence of anti-inflammatory principles produced in the maturation process by thermophilic algae [47].

4.2. Physical Rehabilitation with Electrotherapy

Hermann Munk (1879) is credited with the first experience of transferring medication with the aid of electricity. After 20–25 min of exposure to a strychnine solution, he observed spontaneous cramps in rats. Forty years later, Stéphane Leduc described methods for administering salicylic acid, using electrical current to relieve pain and accelerate wound healing [23].

Currently, there are several technologically safer electrotherapy equipment types available on the market, promoting iontophoresis as an easy method to be applied by therapists and with improved clinical advantages. The considerable challenges in this area are in the development of portable, low-cost devices and semi-solid formulations compatible with the device and the skin [24].

The mechanisms involved in iontophoretic transport are electromigration, the movement of ions through the membrane (skin) from the direct action of an electric field and electro-osmosis, the volume of flow induced by the current [23]. The prerequisites for

delivery management include good electrical conductivity, good mechanical properties, good bio-adhesion, and acceptable viscoelastic properties that guarantee clinical efficacy and patient compliance [24]. There are countless scientific studies associated with the effects, advantages, and disadvantages in the application of drugs through the skin, using iontophoresis.

Alexander et al. (2012) reviewed recent studies carried out with various transdermal drug delivery systems, including iontophoresis, having verified that in most of these studies there are still some inconsistencies regarding the release of the drug, prevention of the sudden release of the formulation and problems related to toxicity, highlighting the need to continue carrying out studies and to develop techniques that successfully promote TDD [48]. Most of the studies aim to compare and verify the effectiveness of treatment protocols, techniques, and complementary treatment activities, and validate the efficacy and tolerance of the drug used.

Some iontophoresis studies using inorganic cation solutions revealed improvements in patients in the treatment of specific pathologies (Table 2).

Table 2. Inorganic ion in iontophoresis.

Inorganic Ion	Pathologies	References
Copper	Mycotic infections	[49,50]
Magnesium	Bursitis	[51]
Lithium	Gouty arthritis	[52]
Silver	Osteomyelitis, rheumatoid arthritis/antibacterial	[53]
Calcium	Dentinal hypersensitivity/osteoporosis	[54,55]
Zinc	Wound healing/antiseptic	[56,57]

5. Discussion

Concerning the European Regulation for cosmetic products and the European Directive for medicinal products, peloids are natural products with cosmetic or medicinal purposes, and in this context, they should be considered borderline products. However, the complexity of this concept and the boundary between regulations, and the prevalence of the principle of non-accumulation of regulations, determine as a key criterion the definition into which a product can fit.

Considering the safety assessment of these products in accordance with Annex I of Regulation (EC) No. 1223/2009, the general toxicological profile of ingredients and the final product should be carried out. For establishing the rationale, based on the information collected and conclusions about product safety, the safety requirements should reflect the quantitative and qualitative composition of the raw materials, important for the establishment of the toxicological profile, their physicochemical characteristics, presence of impurities and trace elements and the risk of exposure to prohibited substances [58]. In addition, the microbiological quality and undesirable effects that could be found are important.

Regarding the presentation of peloids as having therapeutic properties, they can be considered a medicinal product if they also have pathological significance. This is the condition for the case-by-case decision but still taking into account the characteristics of the peloid, its composition and pharmacological properties, and the risks which its use may entail. Experiments in vitro may support the understanding of the physiological mechanism by which application of mud cataplasms relieves pain in rheumatic patients or heal wounds.

The medical hydrology clinical trials also offer scientific support for the medicinal significance of peloids, although the quality of evidence should be improved. It will be necessary to promote the evaluation of the long-term effects to support the therapeutic efficacy as well the specific biochemical effects that allow the distinction between therapeutic peloids. The transdermal drug delivery (TDD) research has had a significant technological

evolution in the presentation of innovative solutions interrupting the skin barrier function (s.c.) and allowing the safe delivery of medicines [59].

Thermalism and physical medicine use specific methods in the rehabilitation, therapy, and prevention of numerous diseases, sometimes being the continuation of outpatient and hospital treatments for chronic diseases that require rehabilitation treatments. Balneotherapy is quite common in the treatment of rheumatic and dermatological diseases. The mechanisms by which immersion in mineral or thermal water or the application of peloids relieves pain in rheumatic patients is not yet fully understood. Probably, the combination of factors such as mechanical, thermal, and chemical effects will be behind these benefits. According to the gate-control theory, pain relief can result from the pressure and temperature of the water or hot cataplasm on the skin. The heat stimulus can influence muscle tone and pain intensity, helping to reduce it, as well as muscle spasms. The importance of heat in the transport of essential elements of clays via pores, through their dilation followed by extreme sweating, is how the ionic transdermal delivery and therapeutic effect is predicted.

This passive absorption depends on many factors that can meddle with the ability for each peloids formulation to penetrate the skin and target the affected area in sufficient quantities to prosecute a therapeutic or aesthetic effect. Skin characteristics vary from person to person, with age and skin health integrity, also representing an important limitation to transdermal delivery.

Iontophoresis is also common in the treatment of rheumatic and dermatological diseases and can be physiologically proven by the therapeutic concentration of an ion or medicine. The use of drugs such as diclofenac, corticosteroids or steroids gained widespread efficacy recognition in physical therapy. The therapeutic action of these drugs is well studied through experimental and clinical trials because of the pharmaceutical and healthcare products regulation compliance and post-marketing drug safety reporting. Previous patient health condition evaluation allows the drug, the electrode charge, the electric current dosage, and the time of treatment to be selected.

The TDD of pelotherapy is assisted by temperature and electrically through iontophoresis. Szántó et al. (1998), carried out a custom-made in vitro diffusion cell study with a bentonite previously enriched in Ca^{2+}, using a direct current through a pig skin and demonstrated that using pulsate currents the amount of Ca penetrating through the skin was 5–10 times higher than through passive transport [60].

The low voltage of iontophoresis and the sweat phenomena with pore dilation of pelotherapy allows the use of the same pathways: hair follicles and sweat pores (Figure 2).

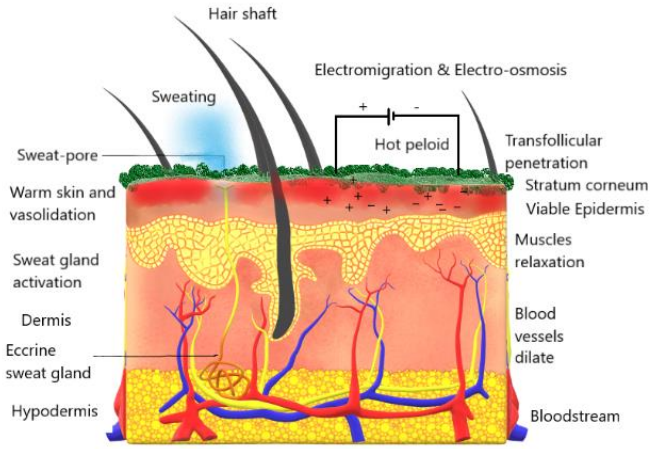

Figure 2. Routes of penetration by electric current and heat (iontophoresis in conjunction with pelotherapy). Adapted from Paint 3D Microsoft ®, Exatronic, lda, Aveiro, Portugal.

6. Conclusions

The therapeutic integration of iontophoresis and pelotherapy focused on patient benefits and low safety-related risk may contribute to the outstanding physiological perfor-

mance of pelotherapy, in way the essential elements and exchange cations pass through the skin and in what circumstances they may reach the bloodstream.

Both methodologies are considered as safe for the patients, supported in clinical evidence. They have undergone clinical trials with scientific recognition, important for therapeutic validation. In addition, the medical device industry is technologically scaling up and focused on safety and product compliance.

Clays are naturally ionized and it is possible to change their polarization using electrolytic solutions or blending them with specific medicinal-mineral water (maturation process). The transdermal delivery activation by electrokinetic forces should be studied considering experimental factors such as current strength (0.5 mA/cm^2), temperature (40–45 °C) of application, time of application (15–20 min) and electrode materials selection. This is possible by developing an electronic device and a skin electrode specifically to store and heat the peloid (Figure 3), to be approved for clinical use [61].

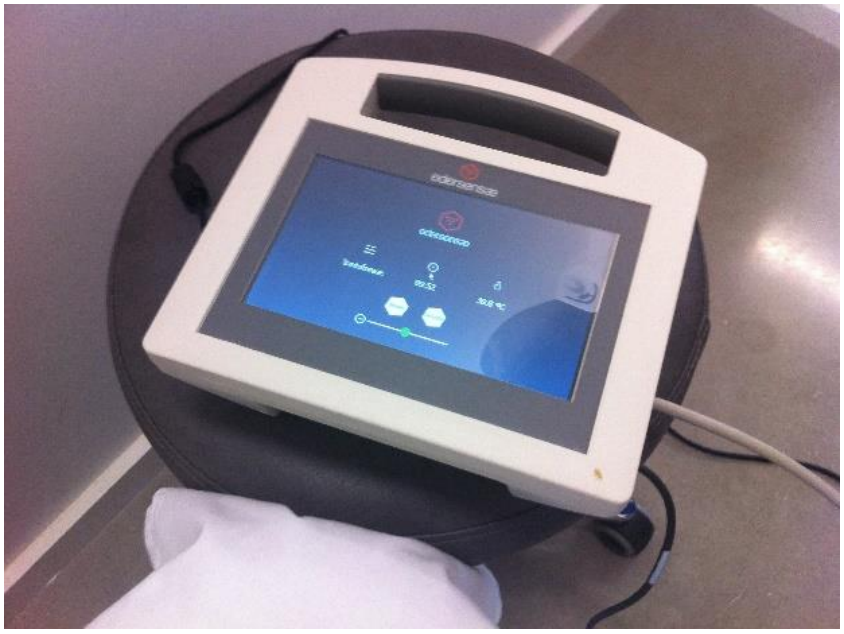

Figure 3. ElectroPelotherapy device (edersensae®), prototype developed by Exatronic, Lda, Aveiro, Portugal.

Clays and mineral medicinal water should be characterized as raw materials and the resulting peloid characterized also as a product, corresponding to what is presented in cosmetic and medicinal product regulation as safety requirements.

The complementarity between pelotherapy and iontophoresis is centered on the main strategy for increasing the transport of substances through the skin. In this new process, the use of an electric field should be investigated which drives a constant low-intensity current combined with temperature, in a peloid causing electrostatic repulsion and/or electro-osmosis, inducing permeability changes in the skin.

The methodology suggested for the safety and quality compliance of peloids and their use in drug delivery, by heat and/or electrical stimulation can be represented in four parts:

Part 1. Establishment of the peloid's toxicological profile and quality requirements performance: mineralogical, chemical, and biological characterization. Characterization of the physicochemical, technological, and heat properties.

Part 2. Microbiological quality control.

Part 3. Physiological significance: Diffusion kinetics and permeation concentration of human stratum corneum. Perspiration absorption.

Part 4. Electrochemical behavior of ions and electrical impedance of peloids while in contact with skin.

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