

The Elegant Resolution for Fat Accumulation and Cellulite Reduction by Sinclair LipoElim™ Treatment

Inna Belenky (Ph.D.)

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INTRODUCTION

Noninvasive body contouring is one of the most appealing segments of esthetic procedures today. Professional body shaping procedures refer to a range of techniques that include size and weight reduction as well as more superficial improvements such as toning, firming and smoothing, with cellulite reduction.

Cellulite is a common skin condition characterized by an irregular dimpling of the skin, which is mainly found on the thighs, buttocks, and abdomen [1]. Although the cause of cellulite remains unknown, its etiology is considered multifactorial, including structural, genetic and endocrine abnormalities. It is evident that weakened connective tissues, enlarged fat cells and diminished microcirculation play key roles in the pathophysiology of cellulite [2].

A variety of energy-based, massage-based and surgical procedures, including subcision and liposuction have been employed to improve fat accumulation and cellulite by promoting microcirculation in the affected areas, loosening the fibrous septae of the subcutaneous tissue, and stimulating the lymphatic drainage [3]. Patients, however, are still looking for safe alternatives without having to undergo surgery or minimally invasive procedures. Several technologies have emerged to address these concerns and propose a noninvasive, transcutaneous delivery of energy for lipolysis [4]. One of them is use of electro-mesotherapy based on electroporation which involves the application of high-voltage pulses to induce skin perturbation [5]. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e., small molecules, proteins, peptides, and oligonucleotides), including biopharmaceuticals with a molecular weight greater than 7 kDa (the current limit for Iontophoresis) [6].

Mesotherapy treatments have been used for body contouring throughout the last decades, involving injections of very small amounts of naturally occurring substances and minerals into the fatty layer. Contrary to classic mesotherapy, the use of electro-mesotherapy does not involve a series of injections that may be painful or cause unsightly bruising and other side effects.

DERMAFUSE® DESCRIPTION

DermaFuse® is a needle-free energy-based device that enhances delivery of Sinclair's all-natural, high-quality topicals for a wide range of skin conditions, including wrinkle correction, skin rehydration, firming and toning, skin lightening, acne clearance and more. DermaFuse® is based on precise science and biochemical processes with a specific, proprietary algorithm called **IonFuse™**.

IonFuse™ properties of electrical current lead to a structural rearrangement of the skin or fat cell's lipid bilayer to form microchannels in the cell membrane. These microchannels enable the passage of natural nutritional compounds and extracts into the skin to enhance biochemical processes. Microchannels are short-lived and reseal soon after compounds are infused. Since the DermaFuse® uses low energy electrical current, the treatment is completely safe without pain or downtime. The system offers the widest range of pulse delivery (100 levels) for individual comfort, and can be used on all skin types.

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All of Sinclair's DermaFuse® serums are created from pure, high-quality, natural ingredients to maximize cell penetration. Each formula is a precise blend of special serums, proteins and healing agents to be used with the Infusion™ system to attain optimal results and the **LipoElim™** Serum is no exception.

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The water serves as a medium for electrical current and glycerin increases the serum's viscosity, allowing the convenience of serum application over the skin and preventing its natural evaporation and waste during the treatment.

1. Hydrolyzed Collagen

High Purity marine-derived collagen from deep water fish is a powerful firming agent. This collagen has a lower content of the polar amino acids' proline and hydroxyproline and therefore has a unique amino acid composition. This collagen is highly compatible with skin and improves the moisture content of skin due to its film forming and moisture binding properties. This collagen also provides anti-irritant benefits.

2. Sodium Hyaluronate

Hyaluronic acid is one of the main components of the extracellular matrix. It maintains skin hydration and suppleness thanks to its ability to retain water leading to added softness and suppleness of the skin. This ingredient is produced by fermentation of a lactic bacterium on a plant substrate.

Both Hydrolyzed Collagen and Sodium Hyaluronate (the Hyaluronic acid) agents provide the skin with a firmer, tighter appearance while diminishing the look of "orange peel skin" in the cellulite as well as providing extra tightening during the contouring purposes.

3. ADIPOLESSTM [7]

INCI Name: **Butylene Glycol & Chenopodium Quinoa Seed Extract**

It's one of the most effective and innovative high-quality plant extracts that is proven to prevent new fat formation and improved slimming efficacy. This unique Canadian Quinoa is obtained through an organic source and patented extraction process. It contains rich bioavailable minerals (iron, magnesium, zinc and manganese), vitamins and essential amino acids.

ADIPOLESSTM extract with a titrated DLP content (dilinoleoyl-glycero-3 phosphocholine) provides a preventative and innovative action against cellulite formation and fat accumulation through an anti-adipogenesis (maturation of new adipocytes) mechanism via the suppression of the MMP-9 signals (see **Figure 1**). The MMP-9 (Matrix metalloproteinase) is secreted by the adipocytes contributing to adipocyte differentiation and neo-vascularization (formation of new blood vessels) (see **Figure 2**). Hence, the anti MMP-9 signal of ADIPOLESSTM extract, suppresses the formation of new fat storage units (see **Figure 3**) and provides anti-angiogenesis effect where formation of new blood vessels for adipocyte nourishment is significantly limited (see **Figure 4**).

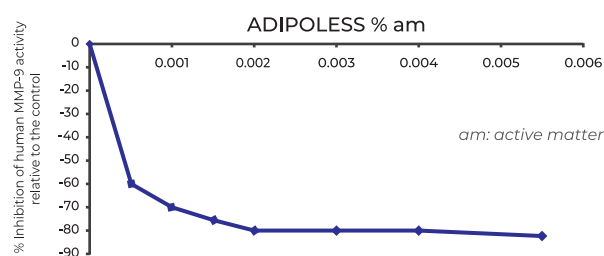


Figure 1. ADIPOLESSTM - Inhibition of human MMP-9 activity is determined by fluoro-enzymatic assay.

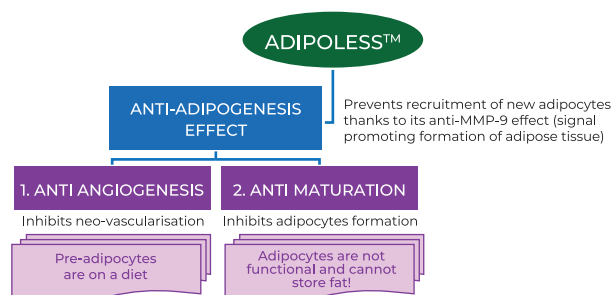


Figure 2. ADIPOLESSTM mechanism.

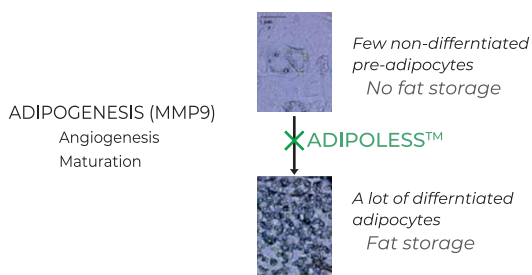


Figure 3. ADIPOLESS™ - anti-adipogenesis effect - inhibition of the formation of new fat cells.

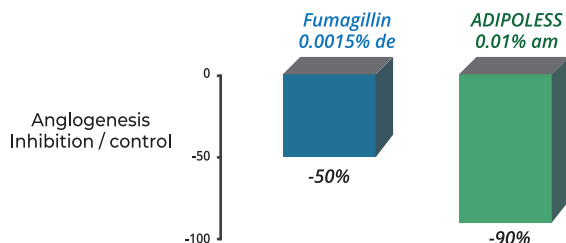


Figure 4. ADIPOLESS™ - anti-angiogenesis effect (neo-vascularization) -100-500% quantification of the number of capillary structures on a UVEC endothelial cell culture coming from cord umbilical (able to arrange themselves in blood vessels).

TREATMENT REGIMEN

When the LipoElim™ serum is used as a standalone treatment with the DermaFuse® device (see **Figure 5**), the average treatment course is about 6-10 sessions, with 7-10 days intervals depending on the initial condition. The recommended maintenance of the results can range between 3 and 12 months, depending on individual's lifestyle, diet, genetics, hormonal fluctuations, etc.



Figure 5. A 37-year-old female before (**left**) and after 4 LipoElim™ treatments (**right**).

Courtesy of Or-Ly Sguiy Aesthetic Clinic (Israel).

The LipoElim™ serum can also be used with Sinclair's Fusion® treatments. Fusion® is Sinclair's unique "combination" treatment solution that provides high level results for skin conditions which typically have low success rate with other technologies or mono-therapy treatments. Taking advantage of the synergistic effect, the Fusion® treatments succeed in generating high-standard clinical outcomes. In synergy, one technology improves the efficiency of the other. Here, the synergy between biochemical components of the LipoElim™ serum and RF energy, produces a more effective, faster and longer-lasting effect in body contouring treatments; since the serum enhances the biological processes (such as lipolysis) following the heat and vacuum stimulation via Sinclair's CORE™ Technology [8].

In case of Fusion® approach, the treatment course can range on average between 3-6 sessions, with a 1-week interval (see **Figures 6-7**).



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CONCLUSION

The extraordinary success of Sinclair's LipoElim™ treatments can be attributed to both the state-of-the-art IonFuse™ Technology incorporated in the DermaFuse® system and scientifically engineered and clinically formulated pure, high quality ingredients, incorporated in the LipoElim™ serum.

Tested with the DermaFuse® system for precise volume and concentration of the active ingredients, it brings safety and unmatched effectiveness. Being sterile, hypoallergenic and non-irritating, the serum can also be applied after minimally invasive procedures, such as fractional RF, microneedling, ablative lasers, and more.

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SINCLAIR

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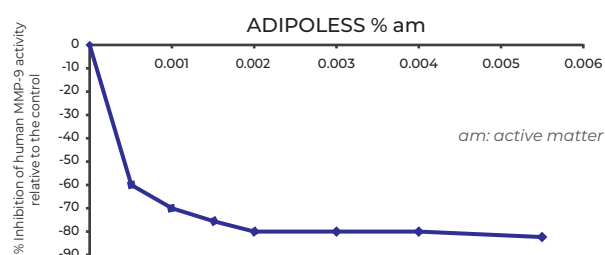


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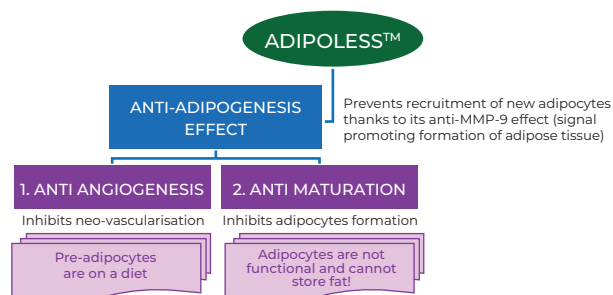


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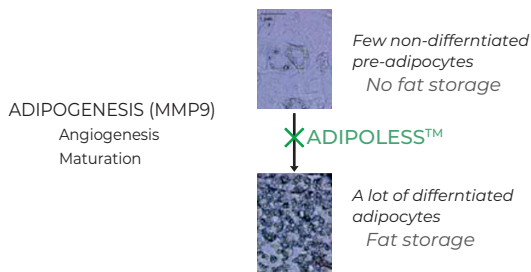


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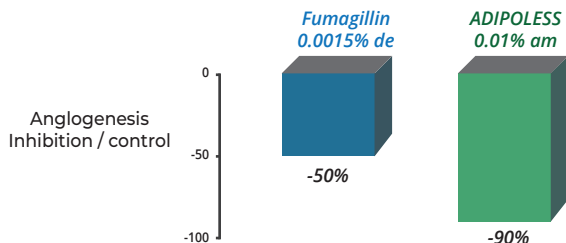


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The truth and myths behind needle-free Mesotherapy - Scientific approach

Inna Belenky (PhD) and Ariel Margulis (M.D., M.Sc.)

Key words: *mesotherapy, non-invasive mesotherapy, needle free mesotherapy, Magnetophoresis, Sonophoresis, Phonophoresis, Iontophoresis. Electroporation*

Abstract

In this publication we conduct broad literature review of scientific publications dealing with different methods of mesotherapy from its beginning to today. The aim of the review was to investigate the nature of needle-free mesotherapy, its history, advantages and disadvantages, different methods and biological/physics background, with a focus on electroporation as the ultimate, safe method.

1. History of Mesotherapy

Historically, mesotherapy (or intradermotherapy) was invented in France in 1952 by Dr. Michel Pistor. Only in 1958 did he publish his conclusions about his experience in his village of Bray et Lu in treating deafness, tinnitus, vertigo, presbyopia and headaches by using local injections of procaine in the article "Review of new properties of topical procaine in human pathology" in the "La Presse Medicale," journal (Pistor, 1976). Although it was Pistor that received the most attention in the "discovery" of mesotherapy, earlier experiments had already been conducted before him. In 1884, ophthalmologist Dr Karl Koller used local cocaine to manage pain, in 1904, German chemist Dr Alfred Einhorn discovered a new anesthetic, procaine (which he patented under the name Novocain), in 1925, Prof Rene Leriche applied intradermal injections in the intercostal spaces and in 1937, Dr Aron published a study about an intradermal injection of a histamine solution (Rotunda and Kolodney, 2006). But actually the history of mesotherapy goes back to Hippocrate (400 years B.C.) who stated that he treated a patient by applying a prickly pear. Thanks to Pistor's publication, in 1958 the French press coined the term mesotherapy and only 30 years later, in 1987 the French Academy of Medicine recognized Mesotherapy as a specialty of traditional medicine (Raghvendra *et al.*, 2010).

However, these days most of the research done on mesotherapy in indexed journals relates to its complications. The most severe and most frequently reported complication is mycobacterial infection, which generally results in unaesthetic scars. Additional common complications reported are: lichenoid eruption, induction of psoriasis, urticaria, cutaneous necrosis, systemic lupus erythematosus, panniculitis, acromia, atrophy and others. These complications are attributed to poor techniques or to the effects of the medication itself (Herrerros *et al.*, 2011). In addition, many people have general fear of needles or cannot afford downtime due to their lifestyle.

These disadvantages have led the medical device manufacturers to develop alternative delivery systems to needle injections. These devices appear attractive to aesthetic practitioners, especially those who are already practicing conventional mesotherapy by injection.

2. Needle-free Mesotherapy Technologies

The highly lipophilic nature of stratum corneum prevents the passive transport of macromolecules across the skin (Flynn, 1989). Extensive research efforts have been aimed towards better understanding the structure of stratum corneum (Mathur *et al.*, 2010). Several publications researched this issue and studied different methods including chemical and physical methods to overcome this primary barrier (Bronaugh and Maibach, 1989; Singh and Singh, 1993).

In general, drug molecules can penetrate the skin by three different pathways (**Fig. 1**):

1. Through the sweat ducts

2. Through the hair follicles and sebaceous glands (collectively called the shunt or appendageal route)
3. Directly across the stratum corneum

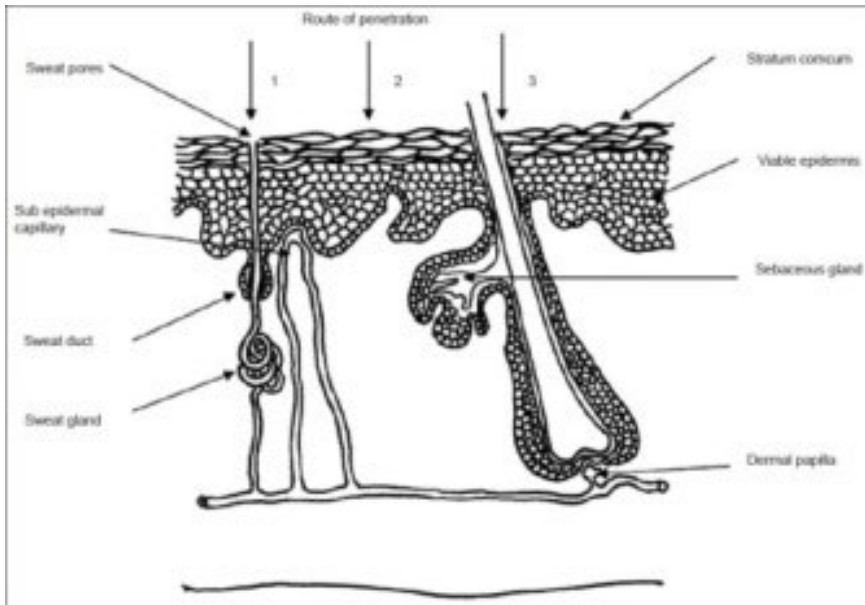


Figure 1: Routes of skin penetration: 1. through the sweat ducts; 2. directly across the stratum corneum; 3. via the hair follicles (Mathur *et al.*, 2010).

The needle-free mesotherapy technologies use one of these pathways, depending on the technology used, leading to differential patient sensation, absorption ability and type of molecules used. Due to these researches manufacturers launched medical devices claiming the ability to deliver topicals through the epidermis and achieve significant penetration in deeper layers of tissue to duplicate the efficiency of a syringe injection. The needle-free technologies include Magnetophoresis, Sonophoresis (Phonophoresis), needle-free injections, Iontophoresis and Electroporation.

2.1 Magnetophoresis

This method involves the use of a low-frequency magnetic field which acts as an external driving force to enhance the diffusion of diamagnetic molecules across the skin. The exposure to magnetic field induces structural alterations of stratum corneum which lead to an increase in skin permeability (Mathur *et al.*, 2010). Several *In vitro* studies were made to study the influence of Magnetophoresis on drug delivery. Murthy (1999) showed a magnetically induced enhancement in benzoic acid flux. Murthy and Hiremath (2001) demonstrated that using a magnet attached to transdermal patches containing terbutaline sulphate enhance permeant flux.

But, the fact that this technique can only be used with diamagnetic molecules make it as limiting factor in its applicability and probably explains the relative lack of interest in the method (Brown *et al.*, 2008).

2.2 Sonophoresis (or Phonophoresis)

This method involves the use of low frequency ultrasonic energy to enhance the transdermal delivery of topically applied drugs (Mitragotri and Kost, 2004). The proposed mechanism has been studied for over 50 years (Mitragotri, 2005). The effects of ultrasound can be described in two ways: thermal or non-thermal effect. Skin absorption can result in significant local heating by ultrasound which accelerate drug diffusion, increase drug solubility, and enhance local blood flow. However, the most significant effect of ultrasound is by cavitation - the growth and oscillation of gaseous cavities (air

bubbles). Collapse of the air bubble results in generation of high pressure shock that are thought to disrupt the stratum corneum (**Fig. 2**) (Morrow *et al.*, 2007).

Ultrasound parameters such as treatment duration, intensity, and frequency are all known to affect percutaneous absorption, with the latter being the most important (Naik *et al.*, 2000). Frequencies at the low range (<100 kHz) are believed to have a more significant effect on transdermal drug delivery, with the delivery of macromolecules of molecular weight up to 48 kDa being reported (Mathur *et al.*, 2010). But Sonophoresis has to overcome its obstacles. Therefore, in order to achieve good results, there is a need to combine with other physical and chemical enhancement techniques like chemical enhancers, Iontophoresis and Electroporation (Rao and Nanda, 2009).

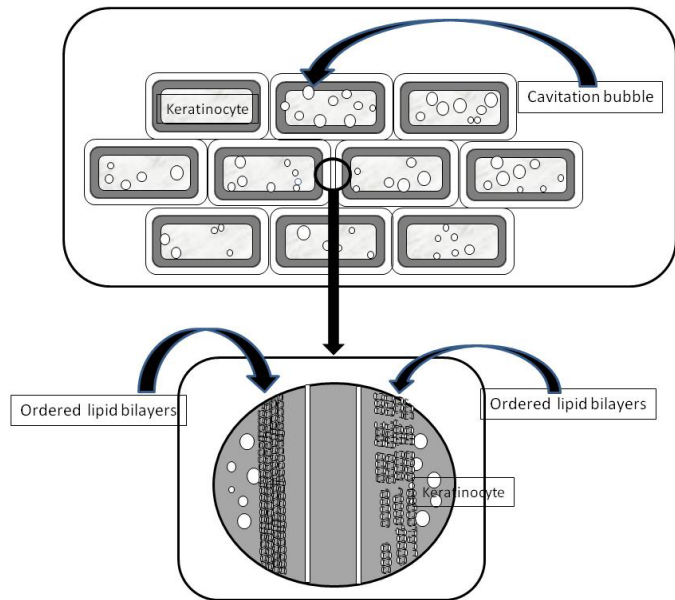


Figure 2: Schematic sketch of cavitation occurring in the keratinocytes. Cavitation occurs preferentially at the interface between the keratinocytes and the lipid bilayers (Escobar-Chávez *et al.*, 2009).

2.3 Needleless injection

In this method transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin by using a suitable energy source through high velocity and high pressure (Mathur *et al.*, 2010). Needle-free injection devices have been accessible to humans since the 1930s (Mitragotri, 2006). Over the years there have been numerous examples of liquid and powder systems (example in **Fig. 3**). The powder systems have been reported to deliver testosterone, lidocaine hydrochloride, and macromolecules such as calcitonin and insulin (Mathur *et al.*, 2010). Problems facing needleless injection systems include the high developmental cost of dosage form and the inability, unlike some of the other techniques, to program or control drug delivery in order to compensate for inter-subject differences in skin permeability. In addition, the long-term effect of bombarding the skin with drug particles at high speed is not known (Brown *et al.*, 2008). Furthermore, since drugs are exposed to high shear stresses during injection, they can adversely affect the structural integrity of big molecules, such as proteins, vaccines and DNA (Mitragotri, 2006).

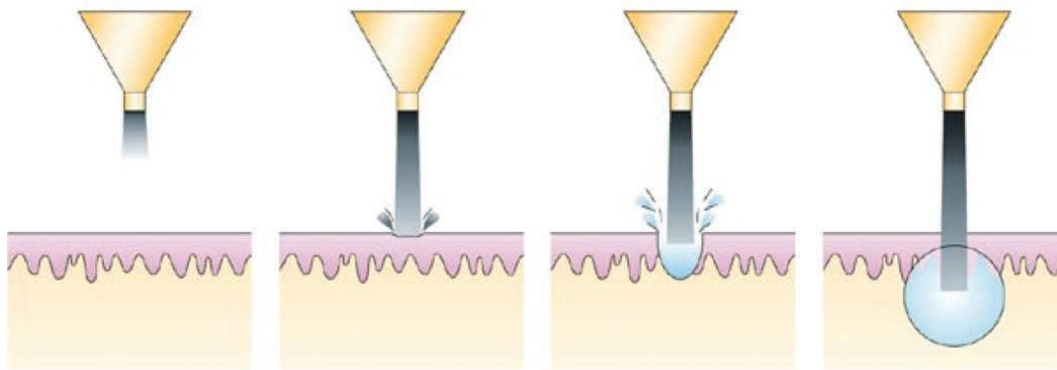


Figure 3: Schematic depiction of the jet injection process. The impact of a piston on a liquid reservoir in the nozzle increases the pressure, which shoots the jet out of the nozzle at high velocity (velocity $>100 \text{ m s}^{-1}$). The jet initiates formation of a hole in the skin. Stagnation of the jet at the end of the hole disperses the liquid into the skin in a near-spherical shape (Mitragotri, 2006).

2.4 Iontophoresis

Iontophoresis is a century old technique and it is one of the two most popular technologies in the aesthetic market. This method involves enhancing the permeation of a topically applied therapeutic agent by the application of a low-level electric current (Galvanic current, approximately 0.5 mA cm^{-2}) (Morrow *et al.*, 2007). An Iontophoresis device consists of a power source, with a positive electrode (anode), and a negative electrode (cathode) (**Fig. 4**) (Morrow *et al.*, 2007). Delivery of a positively charged drug (D^+) can be achieved by dissolving the drug in a suitable vehicle in contact with an electrode of similar polarity (anode). Application of a direct current causes the drug to be repelled from the anode, and it is attracted towards to the oppositely charged electrode (cathode) (Barry, 2001). Equally, delivery of a negatively charged drug occurs when anions (D^-) are repelled from the cathode, towards to the anode (Morrow *et al.*, 2007).

Parameters that affect design of an Iontophoretic skin delivery system include electrode type, current intensity, pH of the system, competitive ion effect, and permeant type. The limitations of iontophoretic systems include the regulatory limits on the amount of current that can be used in humans (currently set at 0.5 mA/cm^2) and the irreversible damage such currents could do to the barrier properties of the skin (Mathur *et al.*, 2010). In addition, iontophoresis has failed to significantly improve the transdermal delivery of macromolecules greater than 7,000 Da (Kanikkannan, 2002). Therefore, Iontophoresis has been used to enhance transdermal delivery of relatively small molecules, including apomorphine, rotigotine etc. (Mathur *et al.*, 2010).

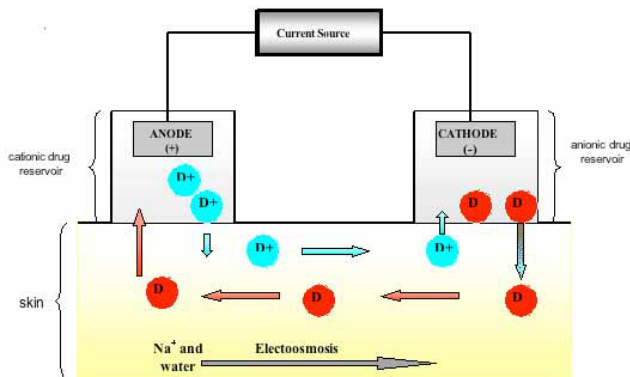


Figure 4: Schematic representation of Iontophoresis. An electrophoretic device consists of a power source, terminating with a positive electrode (anode) and a negative electrode (cathode) (Morrow *et al.*, 2007).

2.5 Electroporation

Together with Iontophoresis, Electroporation is one of the two most popular technologies in the aesthetic market. Electroporation, or electropermeabilization, technology involves the application of high-voltage pulses to induce skin perturbation. High voltages (≥ 100 V) and short treatment durations (milliseconds) are most frequently employed (Bangaa *et al.*, 1999) (**Fig. 5**). Electrical parameters that affect delivery include pulse properties such as waveform, rate, and number of pulses (Bangaa *et al.*, 1999). The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e., small molecules, proteins, peptides, and oligonucleotides), including biopharmaceuticals with a molecular weight greater than 7 kDa (the current limit for Iontophoresis) (Denet *et al.*, 2004; Mathur *et al.*, 2010).

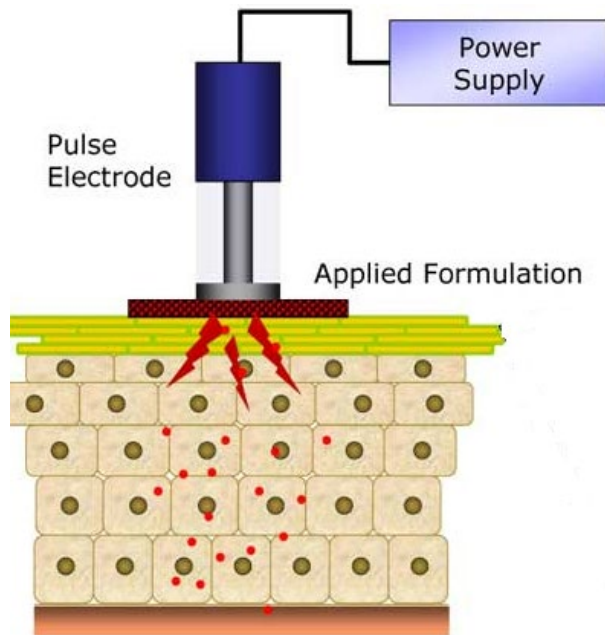


Figure 5: Schematic representation of electroporation (Rolf, 2004).

2.5.1 The process of electroporation

When applying intense transmembrane electric field which exceeding the dielectric strength of the cell membrane, the membrane specific conductance increases (Tsong, 1991). The increase in skin permeability is caused by the generation of transient pores during electroporation (Weaver *et al.*, 1999) which capitalizes on the relatively weak nature of the phospholipid bilayer's hydrophobic/hydrophilic interactions and its ability to spontaneously reassemble after disturbance (**Fig. 6**) (Purves *et al.*, 2001). The pore formation proceeds in three steps: First, upon application of the electric field, water defects appear in the cell membrane. If these defects are stable enough, they lead to the creation of a water file or hydrophobic pore through the membrane. Finally, the phospholipids in the vicinity this pore rearrange to yield a more stable and hydrophilic pore (Le Gac and van den Berg, 2012).

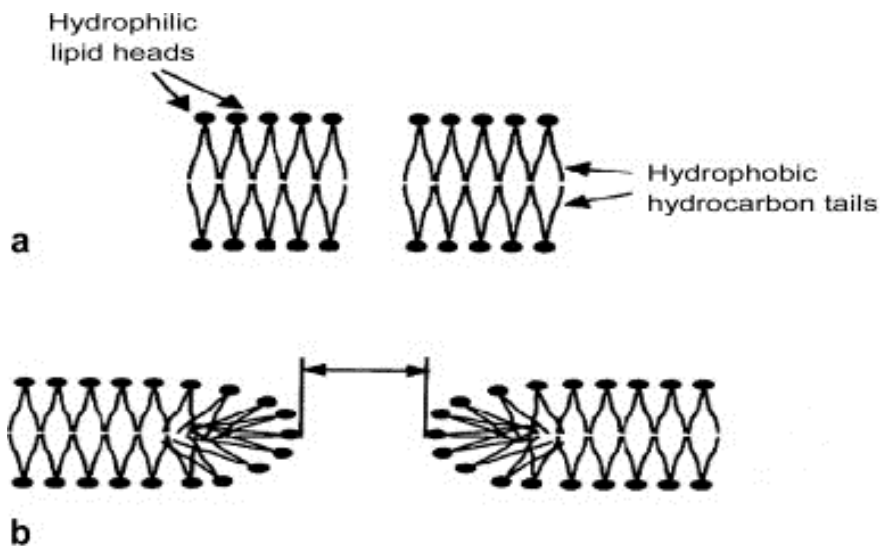


Figure 6. Schematic representation of structures for transient membrane conformations due to electroporation: (a) Arrangement of the cell membrane; (b) following the exposure to intense electric field cell membrane rearrangement occurs with pore formation (Giardino *et al.*, 2006).

2.5.2 Scientific background of Electroporation

The use of electropermeabilization as a method of enhancing diffusion across biological barriers dates back as far as 100 years (Helmstödter, 2001). The development of this method was particularly based on Nobel Prize discovery in Chemistry (1909) by the first physical chemist, Wilhelm Ostwald. Prof. Wilhelm Ostwald proposed in 1890 that the electrical signals measured in living tissue could be caused by ions moving in and out through cell membranes. This electro-chemical idea rapidly achieved acceptance.

Initially Electroporation technology was developed for the introduction of DNA molecules into cells (Neumann *et al.*, 1982) based on theoretical studies and experiments with bilayer membranes in the 1960s and 1970s, by Prof Eberhard Neumann. From the 1980s, the use of electroporation for gene therapy, vaccination, increase uptake in tumours of a chemotherapeutic agent and DNA transformation was published in wide range of publications (Gehl, 2003).

2.5.3 Electroporation versus Iontophoresis

Electroporation reversibly permeabilizes lipid bilayers and involves the creation of aqueous pathways during the application of an electric pulse (Bangaa *et al.*, 1999). In contrast, iontophoresis is believed to primarily transport drugs through preexisting pathways (Cullander, 1992) such as sweat glands and hair follicles (Bangaa *et al.*, 1999). While in electroporation the delivery pathway is intracellular, in iontophoresis the final pathway is intercellular between the preexisting pathways and epidermal cells (Monteiro-Riviere *et al.*, 1994) (**Fig. 7**). Therefore, for the same amount of transferred charges, the drug transport is much higher for electroporation than iontophoresis (Denet *et al.* 2004), increasing the penetration and absorption rate for electroporation, compared to iontophoresis.

Hence the mechanism of transport is different for these two electrical enhancements and therefore the difference in molecular weight limitations. While electroporation is able to deliver molecules with large molecular weight, iontophoresis is limited to 7 kDa.

In addition, iontophoresis's delivery mechanism is limited to charged molecules only, due to its internal physical characteristics as described above, while delivery by electroporation mechanism is limited to water dissolved molecules, including uncharged polar drugs.

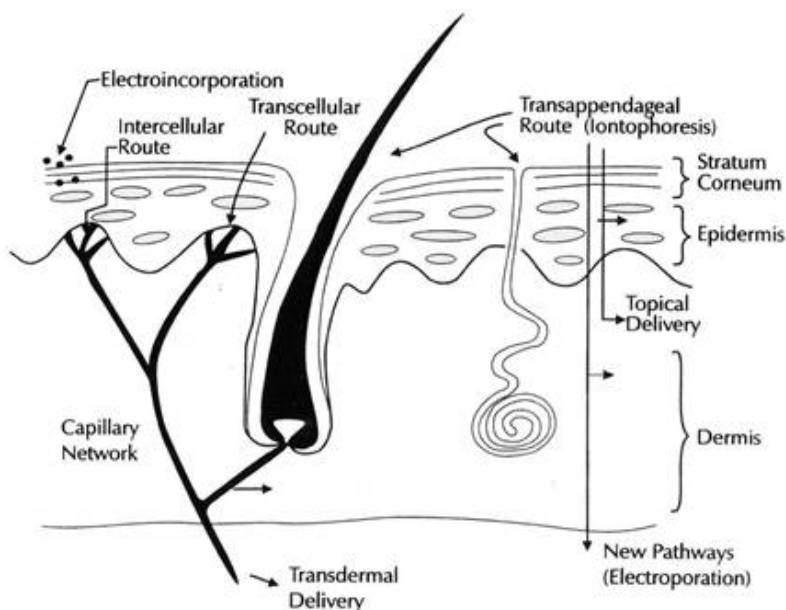


Figure 7: Schematic representation showing the pathways of topical and transdermal delivery, including electrically assisted delivery by iontophoresis and electroporation, (Bangaa *et al.*, 1999).

3. Misconceptions in needle free mesotherapy technologies

In the aesthetic field, there is often confusion in terminology and conceptions. For example, using the term “electroporation” while referring to galvanic current (iontophoresis). This is a very typical and common mistake which results from a lack of differentiation between the terms “electroporation” term and “electrotransport” or “electropermeabilization” which refer to general application of electric current of any type (including electroporation, iontophoresis, etc.)

Additional misuse of terminology occurs in describing pores that are created by electroporation as aquaporins. This common mistakes drives from the fact that the pores created by electroporation are described as aqueous pathways. Once a membrane is charged to electroporation levels, water is forced into the lipid environment. As soon as an aqueous channel is created, the water inside the pore becomes polarized, thereby stabilizing the pore (Neumann *et al.*, 1989). But these aqueous channels are temporary structures in the membrane that have nothing in common with water channels named aquaporins. The aquaporins are a large transmembrane protein family involved in transepithelial and transcellular water movement. These proteins are divided into two groups, those that only transport water and those that also transport glycerol and other small molecules such as lactic acid (King and Agree, 1996). In addition aquaporins are activated by vitamins, steroids and other chemical signals and not influenced by electrical signals as ion channels are. Taken all together these proteins cannot be involved in the delivery of drug molecules.

Another common belief in the market is that all devices based on electroporation technology have the same effectiveness. While all these devices are applying high voltages, they differ in the waveform, rate, and number of pulses (Bangaa *et al.*, 1999). Over the last three decades, electroporation equipment has been refined, where pulse amplitude and pulse length can be independently controlled, for optimization. There are ongoing efforts to optimize delivery of molecules through various technical optimizations, resulting in new equipment available or underway (Gehl, 2003).

One of the best examples of well-established electroporation-based devises is DermaFuse® system (Sinclair, UK). The DermaFuse® system incorporates IonFuse™ technology, engineered specific algorithm which works with the skin cell’s biological processes. The company provides with the system a wide variety of formulas (**Fig. 8**) for different aesthetic treatments such as, anti-aging and wrinkle reduction, collagen regeneration, skin rehydration, skin firming and toning, whitening and acne

clearance. These solutions are created from the pure, high quality ingredients to maximize cell absorption and ensure safety and effectiveness. Each solution is a blend of special serums, proteins and healing agents and is precisely formulated for a skin-specific application.



Figure 8: DermaFuse® treatment solution ampoules

4. Discussion

The search for the ideal skin penetration enhancer has been the focus of considerable research effort over a number of decades. Although many potent enhancers have been discovered, in most cases their enhancement effects are associated with toxicity, therefore limiting their clinical application. In recent years, the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum corneum barrier and the way in which chemicals interact with and influence this structure. A better understanding of the interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicity (Mathur *et al.*, 2010).

For patients that have a fear of needles or are not willing to take a chance with complications and downtime, the non-invasive transdermal drug delivery offers advantages over injection or intravenous administration due to its non-invasive nature, convenience, lack of trauma of the skin and avoidance of first pass degradation or absorption in the gastro-intestinal tract (Kronemyer, 2007). Despite the requirement for higher dosages and series of treatments, a large number of patients still prefer non-invasive treatments over injections with the promise to achieve the same results. Moreover, most of the physicians combine the traditional mesotherapy by injections with needle-free technologies. For example, many dermatologists inject hyaluronic acid to the nasolabial folds and then use non-invasive devices to apply hyaluronic acid, vitamin C, etc. all over the face for general skin therapy.

5. Conclusions

Efficient delivery of materials to a significant tissue depth mandates that the concentration and quantity of topical be maintained without significant dilution. Penetration must therefore be fast and not limited by the sparse distribution of the appendages in tissue. Reality suggests that the technology and method used for delivery is the most important factor in duplicating syringe injection techniques. Therefore understanding technology differences may have a significant impact on a practitioner's choice of equipment and the potential success experienced by patients.

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