

Transdermal Delivery of ionic drug solutions : Innovations and new methodologies.

INTRODUCTION

Transdermal Delivery is not a brand new concept. Along with the years various topical drugs have been modifying their properties to enter the skin more surely but, for many of them, their low capacity to be transdermally delivered, limited the final action. In addition to those drugs new technologies such as DC Iontophoresis, electroporation technology and Ultrasounds ,for instance, have been setting standards for years but they could not hide their own technological and practical limitations especially when trying delivering big-sized molecules and, surely ,in the field of patient's comfort during sessions.

Existing technologies for Transdermal Delivery of products

Various technologies, going beyond chemical penetration enhancers, have been trying to better bypass the barrier function of the skin - stratum corneum - to allow a better delivery of drugs into the dermis.

1) Microdermabrasion opened the way to transdermal delivery Vs topical application methodology. Using microdermabrasion a level of penetration twice than a topical application can be reached (Fig.1).

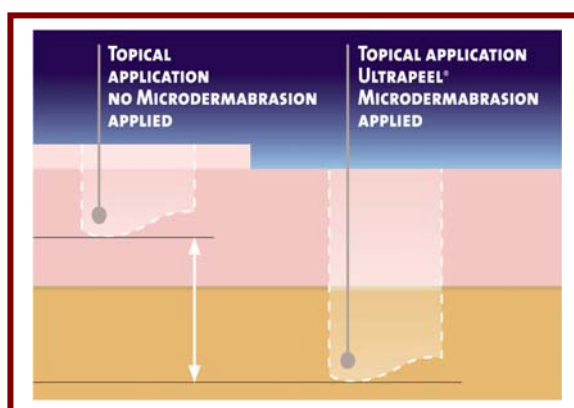


FIG.1 – Transdermal Rate achieved with Microdermabrasion

2) **Traditional Iontophoresis**, it's a process to enhance the penetration of ionized substances into or through a tissue by the application of an appropriate electrical potential (*Singh et al., 2001*). Traditional Iontophoresis has always been fascinating technology manufacturing companies along with patients that “**do not like needles at all**”. Traditional Iontophoresis is based on the fact that “many compounds are composed of positively and negatively charged ions. When these compounds are placed in an appropriate solution, they dissociate into their polar components and assume a + or - charge. While in a charged state, each ion can be influenced by an electrical field created within the solution. + charged ions (cations) will be attracted to the – pole (cathode) and repelled from the + pole (anode) and vice versa. The electro repulsion of like charges is the driving force for Iontophoresis. - *Muslimah Rashed, SPT-Wayne State University Graduate Seminar Nov. 6, 2002.*

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3) The “electrotherapeutic technique” uses a **galvanic current** to "push" a drug (active substance) into the patient's skin. The active substance (negative or positive) is applied over the electrode that has the same polarity (cathode or anode). The ions will migrate into the skin as a result of the repulsion of the similar electrical charges. However, the **electrolysis** reaction at the site of the electrodes (Fig.2) causes a degradation of the molecule being inserted. Furthermore, the substances are mainly absorbed at intracellular level, with poor delivery of macromolecules. Since the galvanic current increases the skin's temperature and may produce burning feeling, it is generally accepted that traditional Iontophoresis may be uncomfortable for the patient.

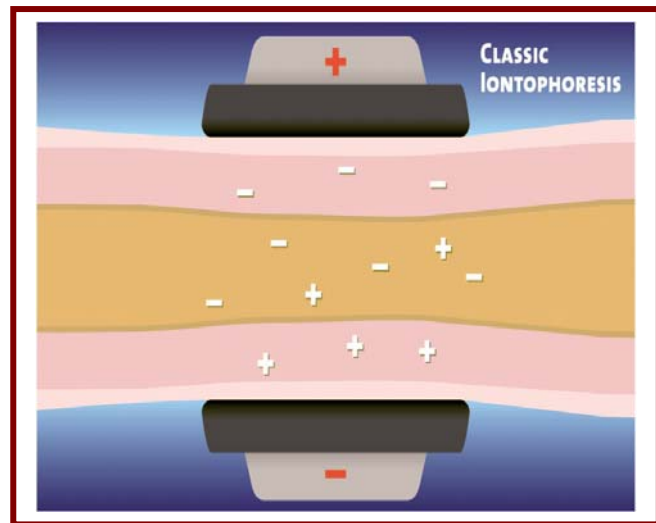


FIG.2 – Traditional Iontophoresis electrolysis effect

4) Ultrasound, instead, allows the drug to be absorbed into the skin through the vibratory movements of the cells caused by the ultrasonic waves. Absorption of the substances is limited to the **infra-cellular space**. As well as traditional Iontophoresis, the Ultrasounds don't allow the delivery of big molecular size and high weight substances. Consequently, the active ingredients (micro molecules) would be absorbed anyhow by the tissues, so the Ultrasounds cannot achieve big sized molecules delivery.

5) Electroporation utilises **high voltages** to “porate” the stratum corneum in order to transdermally deliver the active principle. In spite of the big sized molecules deliverable with this technology , due to the high voltage engaged with this methodology, electroporation may cause in patients some discomfort during sessions and side effects associated to inflammatory localized phenomena.

The Latest Innovations in Transdermal Drug Delivery .

One of the big problems of transdermal delivery is the macromolecules delivery and to decrease the side effects associated to the methodology , especially if the treatment lasts for many minutes. Learning from experience , Mattioli Engineering of Florence - Italy developed a new methodology using the new **Dermoelectroporation®** technology.

Transdermal delivery is a two step procedure:

1- Microdermabrasion –To prep the skin for **Dermoelectroporation®**

Ultrapeel® Microdermabrasion System is well known in the medical community as the first microdermabrasion system that got FDA in 1996. As reliable device as it is, Ultrapeel® Microdermabrasion System performs a uniform controlled exfoliation of the stratum corneum (Fig.3). This condition allow ionic drug solution to be absorbed about twice than a classic topic substance application on skin and ensures reproducibility due to standardization of the thickness and permeability of the stratum corneum. Microdermabrasion is allowed due to the absence of temporary pH change from Transderm Ionto System.



FIG.3 – Microdermabrasion

2- Dermoelectroporation® - To administer the ionic drug solution to the patient



FIG.4 – Transderm Ionto System : Avoids Electrolysis effect delivers both the positive ions and negative ions into the body as an injection does.

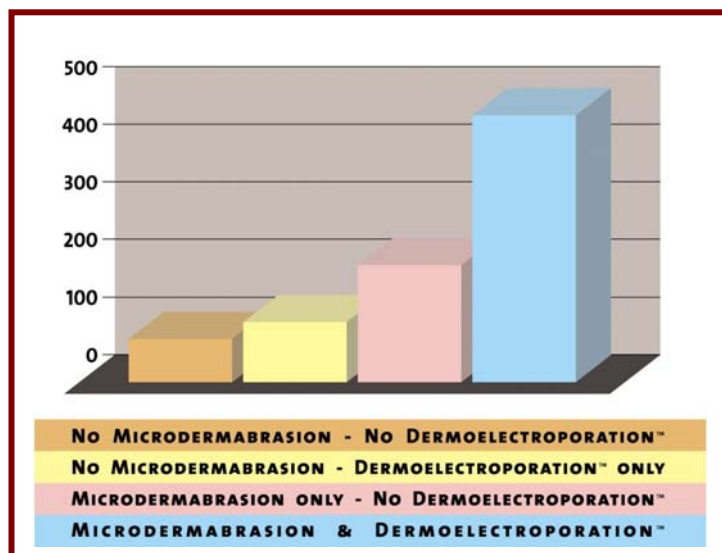
Dermoelectroporation® technology causes the skin to create “channels” to allow ionic drug solutions to penetrate due to controlled “electroporation-like” continuous reversed polarity electrical pulses increasing the skin permeability and allowing transdermal delivery of drugs as occurs in classical iontophoresis, even if the average current value is zero. This pulsed iontophoresis with safe, current-limited, pulsed “Electroporation-like” waveforms allows either micro-molecules and **macro-molecules** to be delivered into the body **without either modification** of the ionic drug solutions pH **and avoiding** either electrolytic effect at the electrodes and electrolysis of the ionic solution itself.

Dermoelectroporation® Technology has no effect on the ionic drug solution being inserted. It takes less time Vs traditional iontophoresis devices to deliver the same amount of ionic drug solution and does not need any skin pH-Compensating patch because does not causes irritation on the skin.

Dermoelectroporation® Technology when combined with **microdermabrasion**, it boosts the transdermal delivery rate to get a higher flux than normally obtained from a Topical application (5 times the topical Application – see Fig.5)

FIG.5 – Delivery rate graph:

Using both microdermabrasion and Dermoelectroporation Technology it is possible to get to a delivery rate 5 times greater than a topical application.



Dermelectroporation® device : Transderm® Ionto System

Transderm® Ionto system is a powered drug-delivery system that has been FDA approved for the “*local administration of ionic drug solutions into the body for medical purposes and can be used as an alternative to injections*”. The whole system, which combines traditional microdermabrasion with Dermelectroporation™, is designed to provide the benefits of transdermal drug-delivery treatments without the limiting side effects of other traditional techniques.



Transderm® Ionto system uses **Dermelectroporation®** Technology to deliver Ionic drug solution into the body and when connected to Ultrapeel® microdermabrader allows a very efficient **transdermal delivery of products**.

Advantages with Transderm® Ionto System.

Capability of Transdermal Delivery of ionic solution of drugs.

Capability of Transdermal Delivery for the first time ever of ionic solution of macromolecules.

No electrolysis of ionic drug solutions.

No variation in the ionic drug solution pH.

Both positive and negative ions of the drug are transdermally delivered at the same time.

Promotes transdermal delivery rate by means of microdermabrasion and pulses delivery.

Reproducibility of dose delivered due to preliminary microdermabrasion.

Vibration feature to minimize the electrical pulses perception on patients.

Non-Invasive action. No trauma from injections.

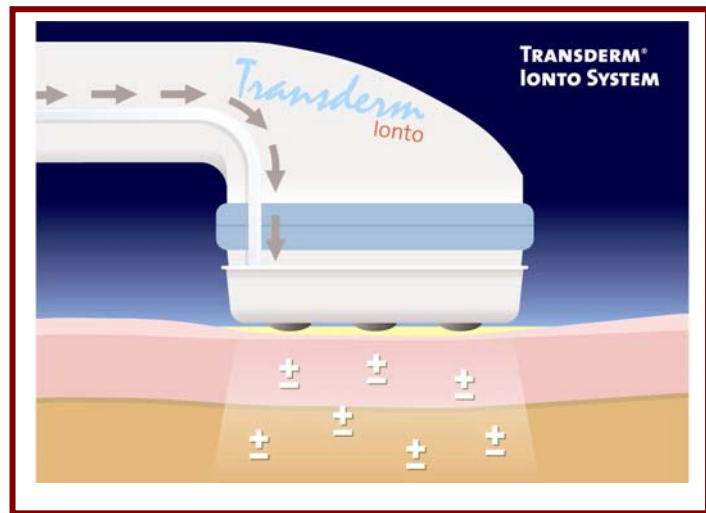
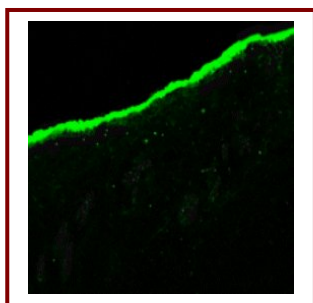


FIG.3 – Transderm Ionto System : Avoids Electrolysis effect delivers both the positive ions and negative ions into the body as an injection does.

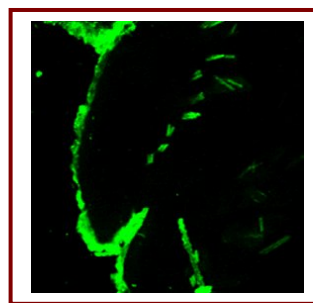
European Experience

Doctors in Europe have been using **Dermaelectroporation®** for over four years, and classical Iontophoresis for more than 20 years, with a variety of substances and drugs. The devices are CE approved and authorized by the Ministry of Health. In Europe, it has been verified that substances such as collagen, elastine, amino acids can be successfully delivered into the dermis via **Dermaelectroporation®** giving great benefits to patients. Clinical studies in **Europe** have shown considerable advantages with this practice. Literature on such topics is available.

Studies have been performed on Dermaelectroporation™ at a variety of universities. The University of Florence, for instance, has proven the great effectiveness of Transderm® Ionto when macromolecules such as collagen are transdermally delivered.

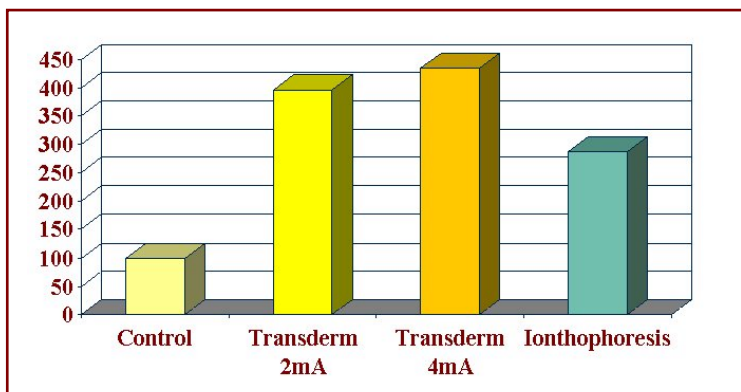


Untreated rat skin; the skin surface appears uniformly covered by a fluorescent stratum while no fluorescence is present in the dermis. 150x.



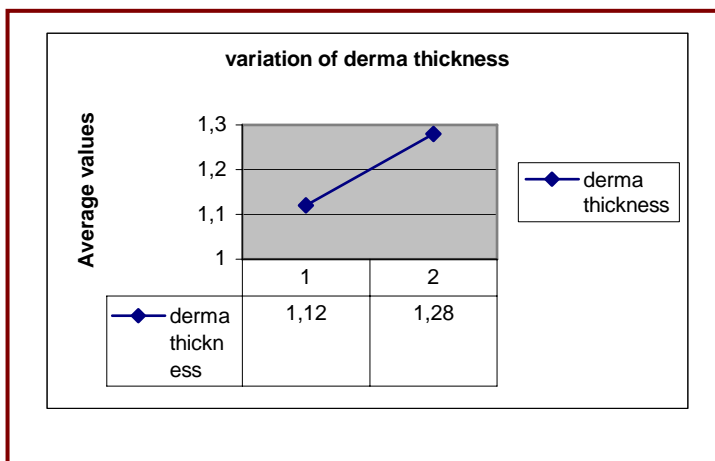
Rat skin treated by "Transderm". The skin surface appears uniformly covered by fluorescence; numerous molecules of fluorescent collagen are observable from the outermost part to the inner part of the dermis. 150x.

Even some others molecules such as Lidocaine and big ones like Heparin have been successfully delivered.



The University of Siena also performed a study on the use of the equipment to improve dermal thickness, reduce wrinkles and enhance vascularization in presence of acne and other scars so that the use of Dermoelectroporation™ in Europe can be summarized into the following applications:

- Photo aging *
 - Photo damage*
 - Post Acne Scars *
 - Hyper pigmentation*
 - Cellulite *
 - Sports Medicine*
 - Rheumatology *
 - Anti-inflammatory & analgesic therapy *
 - Phlebology *
- (*Indication of use not yet cleared by FDA in the USA)

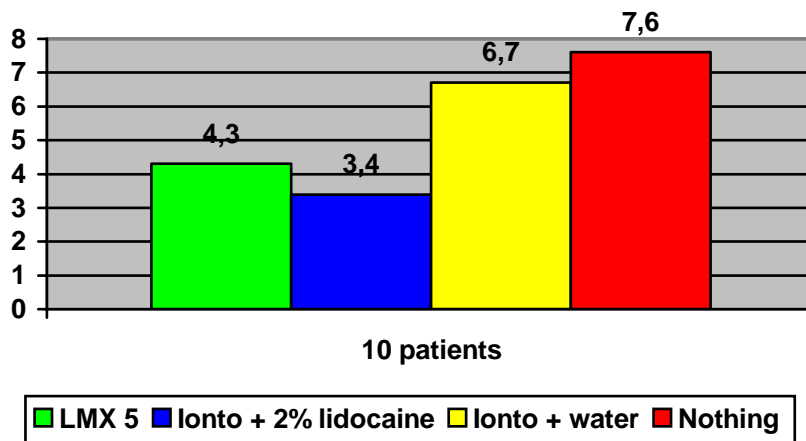


BIORESURFACING WITH DERMOELECTROPORATION TREATMENT Facts observed during treatment - Prof. Pier Antonio Bacci MD , Professor of Aesthetic Surgery in the School of Surgery Specialization University of Siena (Director Prof. S. Mancini)

US Status

The Transderm® Ionto is a powered drug delivery system that is indicated for the local administration of ionic drug solutions into the body for medical purposes and can be used as an alternative to injections.” FDA stated so the first indication of use in the USA is the same as the classical Iontophoresis device, i.e. – topical Anaesthesia with 2% Lidocaine HCl - 1:100.000 epinephrine. Some trials proven that Transderm® Ionto system has been successfully used to deliver 2% Lidocaine HCl - 1:100.000 epinephrine on patients with the following results:

“The results obtained from the Transderm Ionto with lidocaine were statistical significant vs. the topical anesthetic cream ($p < 0.01$) and all the other treatments ($p < 0.001$). The results clearly show that the Transdermal Ionto device can effectively allow the penetration of lidocaine into the skin at those settings and can be used as an anesthetic device to minimize potential pain and discomfort during dermatological cosmetic procedures. These results warrant future studies with different parameters for optimization of pain management and reduction of treatment discomfort.”



Brand New Horizons

Although many barriers are still present in considering the use of transdermal delivery devices kind of difficult, Transderm® Ionto System has been tested very positively with big size molecules and it looks forward to deliver compounds with a very high molecular weight (from hundreds thousands of Dalton in size). This may locate the device in a very interesting position in light of further not-invasive applications.

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