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Characterization of human skin impedance after electrical treatment for transdermal drug delivery

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ABSTRACT

A measurement technique based on Electrical Impedance Spectroscopy (EIS) aimed at discriminating electrical effects of the electrical treatment from the electrical characteristics of drug delivery in human skin is presented. The technique turns out to be useful as the first and most crucial step in determining the drug delivered into the skin after electrical treatment. After recalling the background of electrical measurements principle and electrical modeling of biological tissues, the proposed measurement procedure is illustrated. Then, experimental tests of *in vivo* characterization of the procedure are reported, and the obtained results are discussed.

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1. Introduction

Delivering drugs through the skin is a desirable alternative to traditional methods (oral, injection, etc.) [3,7,26,32]. The active principle turns out to be effective if different layers of the skin are crossed by the drug [4]. However transdermal application are often suboptimal because the transport into the skin is slow due to the resistance of the outermost layer (stratum corneum). Therefore, a variety of physical and chemical methods have been proposed to overcome this barrier [4].

Active methods are proposed to induce driving force and/or to reduce the barrier nature of human skin [7]. Particularly active electrical methods are effective enhancers for drug delivery [8,26]. Among such methods, electroporation and iontophoresis are the of most used [4,7,26,32]. Reversible electroporation is an electrical minimally invasive method to enhance drug delivery through the skin. It differs from the classical purely electrical method, the iontophoresis [4], due to the amplitude of the applied voltage and the derived effects. In iontophoresis, a relatively low-level transdermal voltage (from 0.1 to 5.0 V), or a constant current are used to drive molecular transport [26]. In the electroporation treatment, transdermal electrical pulses with amplitudes ranging from 30 to 100 V [26,32], and duration from 10 μs to 100 ms are applied. This creates a transient aqueous pathway across the lipid bilayer of membranes constituting the stratum corneum and a reversible breakdown of barrier for ionic and molecular transport through the skin [20,26,27,33]. Between these two well assessed technique the application of intermediate voltage (between 5 and 50 V) increases current pathways through the skin elsewhere defined electroporation too [8,34].

However a very important and current problem is the assessment of the real effect of electrical treatment in the outcome of pharmacological therapy [16,18] and the length of pharmacological effects [3,14,15,25,35]. There-

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fore, a critical point is to develop a measurement method for assessing the amount of drug delivered into the skin after the electrical treatment. To this it is preliminary necessary to distinguishing the effects on measured parameters due to two phenomena: electrical stimulation and tissue drug absorption.

With this aim, electrical effects of simultaneous variations in tissue electrical properties due to electrical treatment and to drug transfer can be assessed. Both are largely studied [8,14–16,18,26,32–35], but until now any analytical model and/or an experimental procedure for discriminating between the two different phenomena has been proposed. As a matter of fact the lack of an effective measurement method to asses drug delivery through electrical treatment prevents its successful diffusion at clinical level.

Electrical properties of biological tissues have been characterized successfully by means of methodologies based on the general principle of the Electrical Impedance Spectroscopy (EIS) [1,12,13,24,28,31]. In particular, Electrical Bioimpedance Analysis is one of the nondestructive, low invasive, and most promising instrumental techniques for characterizing biological tissues. Information about electrical characteristics of the tissue are gathered by injecting low-level sinusoidal currents in a given frequency bandwidth by external electrodes (Fig. 1). As a matter of fact, previous studies highlighted the sensitivity of electrical parameters to the drug delivered into the skin by surveying the variation in electrical measurements after the local treatment [9,15,19,35]. However, in proposing the use of EIS for assessing drug absorption after electrical treatment, the twofold problem of discriminating from the measurement results the simultaneous effects of (i) the modification of skin electrical properties due to electrical treatment and (ii) the variations in skin electrical properties arise from the presence of drug delivered into the skin must be faced.

In this paper, a methodology based on EIS measurements able to distinguish the effects of electrical treatment in change of skin impedance spectra and electrical effects of drug delivery inside the skin is presented. A straightforward electrical model and an *in vivo* EIS measurement procedure has been studied and tested experimentally before and after treatment. In Section 2, after the reference to the background of electrical model of biological tissues, the proposed measurement procedure is illustrated. In Section 3 the experimental tests of *in vivo* characterization of the proposed procedure are reported and, in Section 4, the obtained results are discussed.

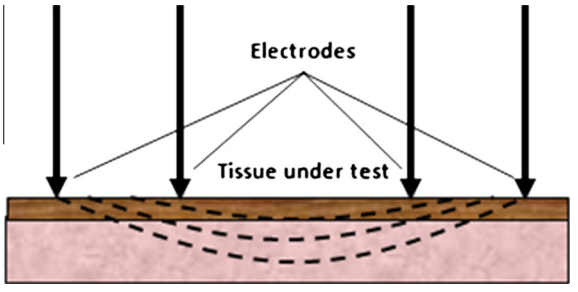

Fig. 1. Electrical characterization of the tissue by injecting sinusoidal currents in a given frequency bandwidth by external electrodes.

2. Method

In the following, (i) the *measurement principle*, (ii) the *electrical model*, and (iii) the *in vivo procedure* of the proposed method for discriminating the electrical effects of drug delivery from the effects specific of electrical treatment are illustrated.

2.1. Measurement principle

Electrical properties of generic biological tissues, and specifically of the skin, can be analytically represented by the well-know model used by Cole in 1940 [24], from which derives an impedance expression of behavior of EIS measurement [28]:

$$Z_{tissue} = Z_\infty + \frac{Z_0 - Z_\infty}{1 + (j\omega T)^\alpha} \tag{1}$$

where Z_∞ represents the electrical impedance of biological tissue at high frequency, Z_0 at low frequency, $\omega = 2\pi f$ (f is frequency), T is the circuit time constant, and α ($0 \leqslant \alpha \leqslant 1$) is an empirical parameter characteristic of the distribution of the relaxation frequencies of the various structures forming the tissue [24,28].

At very-high and very-low frequencies, biological tissues are commonly represented as pure resistors [17], thus the impedances Z_∞ and Z_0 in Eq. (1) can be replaced by the ideal resistor R_∞ and R_0 [17,24]:

$$Z_{tissue} = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega T)^\alpha} \tag{2}$$

An ideal graphical representation of (2) on the complex plane is an arc of circle in the complex plane with the center shifted with respect to the real axis [17,28,31,35], where f_c, the characteristic frequency is given by:

$$f_c = 1/2\pi T \tag{3}$$

The four parameters R_0, R_∞, α, and f_c are required for the characterization of the model of Eq. (2) of biological tissue.

The measurement principle is based on the idea of found the four parameters R_0, R_∞, α, and f_c, that best fit the model of Eq. (2), beginning from measurement data in a given frequency bandwidth.

2.2. Electrical model

The electrical representation of (2) is based on a constant phase angle impedance Z_{cpe} [22,28]. Z_{cpe} is an empirical function commonly used in fitting circuits to impedance spectroscopy measurement. The Z_{cpe} model is used, instead of the traditional resistor–capacitor (RC) model, to take into account the dispersion in cell membranes [28,31]. The impedance of this element is of the type:

$$Z_{cpe} = A(j\omega)^{-\alpha} \tag{4}$$

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