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Non-invasive real-time in-vivo monitoring of insulin absorption from subcutaneous tissues

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Abstract. A non-invasive measuring system for assessing in-vivo and in real time the individual rate of absorption of insulin from subcutaneous tissue has been developed at University of Naples Federico II [1]. In this paper, the method is proved to be a sound reference for insulin therapy. In particular, the proposed measurement system allows to assess if the insulin injected in subcutis is actually flowing into patients bloodstream in due course to achieve the treatment goal. For proving this principle, the previously prototyped and validated portable measuring medical device (DUSM, Drug Under Skin Meter) was revised and an experimental campaign was carried out in order to prove the suitability for insulin therapy.

1. Introduction

Bioimpedance measurement is a medical investigation technology widely used in clinical diagnosis and research [2]. Non-invasiveness, pain-freedom, and safety are the key features for its application success. Its effectiveness in evaluating body composition is claimed by a large number of sector studies [3], [4], pharmacological investigation and pharmacokinetic studies [5].

A recent study of the Authors has proven the suitability of bioimpedance for measuring an amount of drug transdermally delivered in subcutaneous tissue and the suitableness of eggplant pulp in emulating electrical skin behavior [6]. In particular, its ability to explore the subcutaneous tissue in a non-invasive way was considered by pharmacological researchers as an opportunity for some therapies: the progressive disappearance of a systemic drug subcutaneously administered can be monitored, in order to get an indicator for the individual absorption rate. In fact, the drug absorption mechanism depends on a large number of influence factors (age, sex, concomitant medication), thus is characterized by an unacceptable intersubject variability [7]. Moreover, in the event of absorption defects, drug monitoring is required for progressive dose adjustment [8]. Every drug is made of a mixture of one or more active substances and excipients. The active ingredients have the pharmacological activity in charge of healing action, but they act in very very low quantity, and this makes it impossible to administer them without the addition of excipients. So, for the proposed application, the investigation target was changed: effort was up to now aimed at quantifying a volume of drug as a whole, whereas it is now being displaced and addressed to the flow of the sole active ingredient. Aim is now to discriminate the active principle among different concentration levels in the subcutaneous tissue after administration.

This paper contains an overview of the pharmacological application the instrument DUSM is going through, the hardware upgrade that allowed it to confront the feasibility campaign in

vitro, and the promising outcome that encourage to go further down this line of research.

2. Baseline Research

2.1. DUSM Design and Working

The DUSM is basically a spectroscope flexible for clinical application, designed to comply with stringent requirements of current limits for patient's safety, in due regard with the regulatory standard IEC 60601. Hardware is principally based on the chip of Analog Device ADuCM350, a GUI for Windows was developed for presetting controls, launching measurements and storing results in a database. The impedance spectroscope generates a sinusoidal current, injected in the tissue under test by means of two surface cutaneous electrodes. Impedance magnitude and phase are computed and purposely developed algorithms are implemented for converting the information about the impedance variation and providing an accurate estimation of the amount of drug dispensed in the volume under investigation.

2.2. Functional Validation and Metrological Characterization

Instrument performance was assessed throughout an experimental campaign broken down into tests in vitro on eggplant pulp samples, ex vivo on porcine ears, and in vivo on human patients [6]. Best operating conditions were identified and, for measurements carried out on biological tissues, a linear variation of impedance magnitude was experienced in response to increasing amounts of drug introduced.

3. Pharmacological Application of DUSM

Within the new application, the instrument is meant to trace the progressive lowering of drug concentration in subcutaneous tissue by analyzing the tissue impedance time trend. This trend also depends on the drug impedance. Compared to the previous use, the objective of measuring the variation of one of the components of the injected solution poses a sensitivity problem. As first step, operation in a controlled environment, namely, in an electrochemical cell, was carried out, in order to check if, under favorable conditions, the sensitivity of the instrument was sufficient.
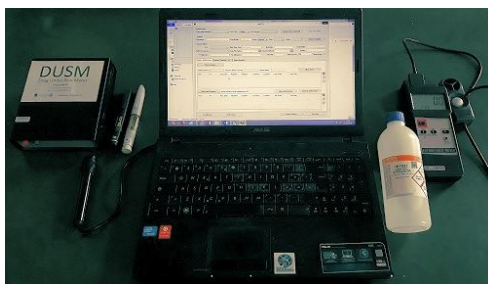

Figure 1. Experimental setup with electrochemical cell and DUSM.

3.1. Hardware Upgrade and Calibration

At this aim, DUSM was equipped with a sensor based on 2-pole electrochemical cell technology. The sensor can realize cell analysis and evaluation through measurement of electrochemical signals. A calibration of the conductivity measuring chain was required to convert conductance readings into conductivity results. It consisted of determining the value of the cell constant under the operating conditions. A standard solution of known conductivity referenced to temperature,

Hanna HI7031L, was subject to measures at a temperature of 26.2°C, with stimulus signal amplitude of 520 mV and frequency of 1 kHz. The resulting cell constant was 0.742.

3.2. Insulin Solution Electrical Characterization

Impedance measurements were carried out on twentytwo distinct insulin solutions, realized using two different pharmaceutical preparations as solute and a saline solvent, in order to reveal insulin electrical behavior. The pharmaceutical products were chosen among all because of their diametrically opposite pharmacokinetics. The first one, Abasaglar by Lilly, contains Glargine insulin, a long-acting insulin analog, the second one, Humalog by Lilly, contains Lispro insulin, a rapid-acting one. For each pharmaceutical preparation eleven solutions were prepared, with concentration levels in saline solvent varying from 0.00 to 100.00 U/ml with 10.00 U/ml steps. The room temperature was of 20.0°C, the stimulus signal features the same set for calibration. For each data set, the best fitting curve equation is reported in (Figs. 2):
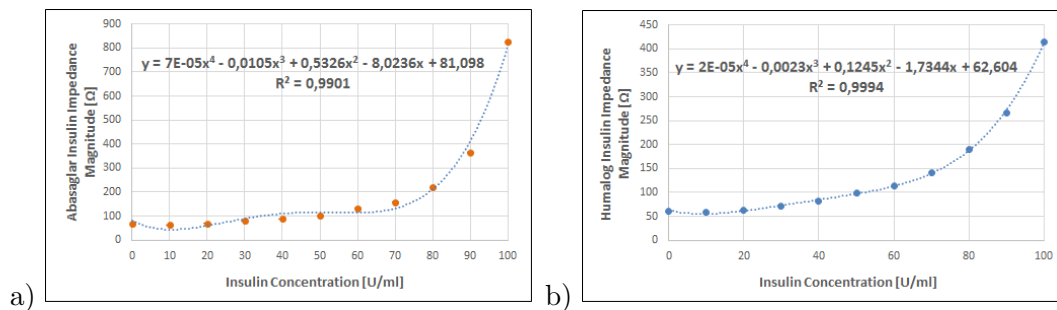

Figure 2. Measured impedance magnitude at varying concentration for insulin solution of (a) Abasaglar and (b) Humalog and fitting curves equations.

4. Feasibility Experimental Tests

The suitability of DUSM for assessing the level of insulin concentration in subcutaneous tissue was empirically proven by the outcome of a feasibility experimental campaign using eggplant pulp for emulating subcutaneous tissue. To analyze the relationship between impedance trend and change in insulin concentration in a biological tissue, it was not possible to use the same approach as in the electrochemical cell. A similar representation (the same measuring points) of the impedance trend for varying insulin concentration levels could have been obtained by using for each drug class eleven different eggplant samples ,each infiltrated with one of the eleven solutions already tested in the cell. Unfortunately, many experiments led us to confirm that uncertainty of inter-individual reproducibility exceeds the effect produced by the variation of insulin concentration. To get around the problem, the experiment was carried out by injecting a succession of constant volumes at a variable insulin concentration in the same sample. Considering that the impedance magnitude variation, normalized to the pre-injection value, depends linearly on the amount of drug[1], the hypothesis of correlating the variation of insulin concentration to the linearity coefficient was formulated.

The drug concentration in eggplant pulp distribution volume was varied by practicing for each sample six consecutive injections of constant volumes of two different solutions of insulin, defined by setup settings such as the two electrodes dimensions and the distance between them. The first three injections were made with a Humalog insulin solution at a concentration of 10.00 U/ml (Fig.3, in blue), for a total volume of 0.15 ml divided into three steps of 0.05 ml, the last three with the same volumes of a solution of the same insulin product at a concentration of

100.00 U/ml (Fig.3, in red). The impedance values of the two injected solutions were significantly different from each other and this was reflected on the tissue impedance decreasing rate. For each sample the impedance magnitude percentage variation values were distributed in such a way that they were best fitted by two adjacent and differently sloped lines. Repeating the same experiment on 10 samples, on average, the slopes of the lines best fitting the first groups of injections were 3.53 times higher than those of the lines best fitting the second ones. The slope variation is qualitatively consistent with the results obtained in the measurements in the electrochemical cell.
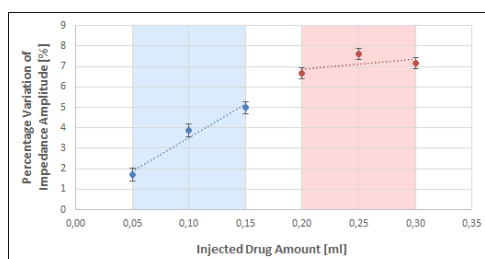

Figure 3. Impedance magnitude percentage variation at varying injected volume for two different insulin concentration solutions: 10.00 U/ml (blue) and 100.00 U/ml (red).

5. Conclusions

The low-cost and low power and consumption portable spectroscope developed at University of Naples Federico II, which proficiency in dermatological applications for assessing the efficiency of transdermal delivery has recently been demonstrated, has now shown its suitability for a new challenging application. It succeeded in discriminating between two different levels of insulin concentration at a fixed depth. However, future in-vivo research perspectives want it to be able to accurately distinguish among concentration levels of insulin in the subcutaneous tissue, with a good resolution and exempting from intra-individual variability affection. Therefore, further exploratory campaigns are needed to provide a rigorous definition for sensitivity and to ascertain whether it matches the research goals deriving from insulin therapy standards.

Acknowledgements

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