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► **To cite this version:**

Yassine Talbi, Eric Campo, Damien Brulin, Jean-Yves Fourniols. Controllable and re-usable patch for transdermal iontophoresis drug delivery. *Electronics Letters*, 2018, 54 (12), pp.739-740. 10.1049/el.2018.0731 . hal-01780138

HAL Id: hal-01780138

<https://laas.hal.science/hal-01780138v1>

Submitted on 28 Aug 2023

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Controllable and re-usable patch for transdermal iontophoresis drug delivery

Y. Talbi, E. Campo, D. Brulin and J.Y. Fourniols

Transdermal active drug delivery is one way to propose new disease treatment as an improvement to passive diffusion by patches based on concentration gradient. Although skin limitations due to low permeability active transdermal delivery approach are investigated, an iontophoretic reusable and controllable patch seems to be interesting solution. Making such an e-health care device provides active control and permanent actuating link able to control the amount of drug delivered. In vitro experiment is conducted to investigate the current effect on the permeation. Modelling and simulations are carried out to optimize the design and the electrical stimulation and finally a global overview of the architecture of the patch is presented.

Introduction: During the past few decades, intensive research has been conducted on transdermal drug delivery system. The transdermal way is considered to be one of the most convenient forms of drug delivery. It offers key advantages over oral route such as sustained delivery, higher bioavailability, minor side effects and better compliance.

Moreover, the global market for transdermal drug delivery is attractive and growing. It generated revenues of more than US \$3 billion in 2010 [1], \$25 billion in 2013 and is expected to exceed \$40 billion by 2018 [2]. However, transdermal route suffers from limitations governed largely by the structure and the function of the skin, in particular its barrier function. Consequently, the drugs that can be administered using conventional patches are generally limited to low-molecular-mass hydrophobic substances. Hence, in order to overcome this limitation, several methods have been developed to enhance permeation and disrupt temporarily the skin to deliver larger molecules. An in-depth review of these methods can be found in [3]. Iontophoresis is the most widely used physical enhancement technique. It refers to the transfer of charged molecules under the influence of an electric field as depicted in 'Fig. 1'. Typically, it involves an application of a low electrical current density (< 0.5 mA/cm²).

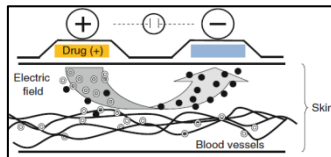


Fig. 1 Iontophoresis principle

Several studies describe the increasing efficiency when using iontophoresis to deliver macromolecule such as insulin in animal models [3] [4], and has been approved by the FDA for the delivery of small molecules in a clinical setting. Activapatch [5] and Iontopatch [6] are two commercially marketed iontophoretic patches used for drug delivery. Nevertheless, they are single-use and offer no possibility of administration control. In this regard, this letter presents a reusable and controllable transdermal patch to deliver precise amount of medication.

In vitro study: an in-vitro experiment was conducted to evaluate the iontophoresis efficiency in comparison with passive diffusion, and highlight the relationship between current intensity and amount of permeated medication.

In this experiment, a porcine skin was mounted in Franz diffusion cells maintained at 37 ± 0.5 °C. 2% Lidocaine hydrochloride was placed in the donor compartment while the receiver was filled with PBS (12 mL). Ag/AgCl wire electrodes were fixed respectively at the donor and the receiver compartments. Three current densities were used, 0.25, 0.5 and 0.75 mA/cm² to study static direct current effect on lidocaine permeation.

At predetermined times (0.5, 1, 1.5, 2, 2.5 and 3 hours), 1 mL samples were withdrawn from the receptor compartment and were immediately replaced by the same volume of the buffer solution (PBS). The samples were injected onto the high performance liquid chromatography 'HPLC' system equipped with Phenomenex Kinetex 5u C18 100A

column (5µm; 250x4.6 mm). The HPLC system consists of an autosampler and a diode array detector. The quantification of lidocaine was performed by integration of the peaks detected at 263 nm. The samples were chromatographed using an isocratic mobile phase consisting of acetonitrile-formic acid 0.1 % (2:8) at a flow rate of 0.6 ml min⁻¹ with an injection volume of 50 µL.

'Fig. 2' shows the cumulative permeation of lidocaine for 3 hours upon different current densities. Passive transport resulted in cumulative amount value of 51 µg/cm². It is generally low, depending essentially on the ion concentration and the diffusion coefficient according to Fick's law. However, applying current densities 0.25, 0.5 and 0.75 mA/cm² resulted in cumulative amount value of 115, 199 and 247 µg/cm², respectively. A linear increase of the permeated amount is observed [7]. In fact, the current represents a driving force for ionic molecules across the skin.

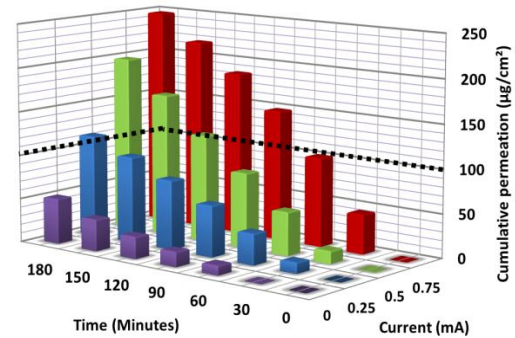


Fig. 2 Lidocaine cumulative permeation for different current densities

More importantly, the linear relationship between current density and permeated amount of lidocaine could potentially be exploited to control precisely the amount of drug delivered based on the intensity of current and the duration of the treatment. For example, 100 µg/cm² could be obtained either in 1 hour at 0.75 mA/cm², 2 hours at 0.5 mA/cm² or 3 hours at 0.25 mA/cm². It is up to user or practitioner to decide the profile of administration needed.

Numerical modelling and simulation: The mathematical model was solved numerically using the finite element technique. Firstly, the modelling of Franz diffusion cell was carried out and results were compared to the experimentations presented above for validation. Then, the model was applied to a planar structure (geometry of the patch) 'Fig. 3'. This was performed as follows: after the design and the meshing of the Franz cell, iontophoretic transport was modelled. Three main physical mechanisms are involved in iontophoretic transport and are considered in the modified Nernst-Planck equation (1): electrophoresis, diffusion and electroosmotic flow.

$$\frac{\partial C_i}{\partial t} = -\vec{\nabla} \cdot \vec{J} = -\frac{D_i z F \vec{\nabla} (C_i E)}{RT} + D_i \Delta C_i - \vec{\nabla} \cdot (C_i u) \quad (1)$$

Where J is the flux of ions, C is the drug concentration, D is the diffusivity, E is the electric field strength, F is Faraday's constant, u is the velocity of the convective flow and z is the charge number.

Furthermore, the heterogeneous structure of the skin was taken into account in the modelling including various biological parameters (conductivity, diffusion coefficient, thickness of layers). 'Fig. 4' depicts the approach followed to validate the modelling of both structures.

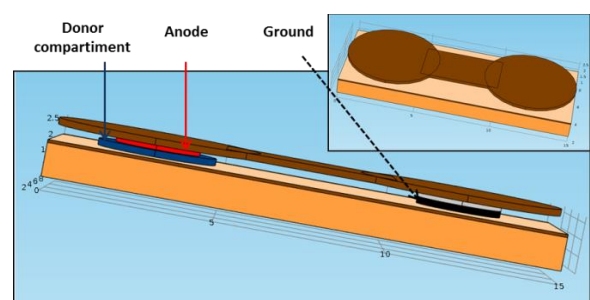


Fig. 3 Schematic 3D of the transdermal patch

