Capacitive Method for Drug Release Monitoring in Dermal Patches

B. Țebrean, S. Crișan, V. D. Zaharia, T. E. Crișan

Faculty of Electric Engineering, Technical University of Cluj-Napoca, Romania

Abstract: *This paper presents the comparative results obtained from functional simulation and practical measurements made for two types of patches filled with a substance. The delivery of the substance in a certain medium is monitored with a capacitive method. The aim of the paper is to confirm the simulation and the mathematical models through a practical, implemented device and to compare two types of patches with different shapes. The paper also contains constructive aspects of the application and some observations regarding the controlled release of a substance included in a patch and how the real conditions can be reproduced in laboratory tests.*

Keywords: *dermal or transdermal drug delivery systems, coplanar capacitors,capacitive sensors, biomedical transducers, biomedical monitoring*

1. INTRODUCTION

The controlled release of a drug in the body is an actual concern of many researchers in medicine, chemistry, pharmacy and other related fields. The patch that contains a substance that must be released in a specific time does not represent a novelty in pharmacy.

Generally, the release time is computed from material and substance properties. As it is well known, every person has different skin texture with a different absorption coefficient. For this reason, sometimes a close monitoring of the delivery process may be needed.

This paper presents the comparative results obtained from functional simulation and practical measurements made on two types of patches filled with a substance.

The delivery of the substance into a medium is monitored with a capacitive method. In this paper two coplanar capacitors will be presented.

In the first part of the paper some constructing aspects will be discussed. In the second part, the results obtained from mathematical modelling and practical tests will be presented.

2. CONSTRUCTIVE ASPECTS

For the experimental devices two patches were built: one circular and one square shaped. Each of the patches has two main parts: the backing with built-in capacitor and a substance layer.

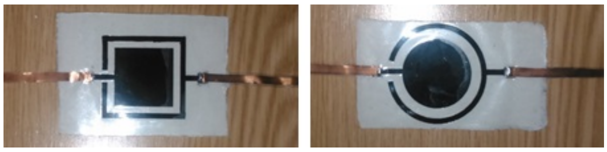

Fig. 1 The experimental patches

The backing with built-in capacitor is made of impermeable polyethylene. The capacitors are laminated into two layers, the total thickness of the capacitive sensor being 0.3 mm.

The capacitor plates are made of copper, with a thickness of 0.1 mm. Two plates are built: voltage terminal – internal one and ground terminal – external one. The interior terminal area in both cases is around 900 mm^2. The square internal plates are 30 mm in length and the diameter of the circular one is around 33.5 mm.

The substance layer is made from cotton cloth around 2 mm thick. The volume of the stored substance may vary depending on the porosity of the material. For this study we have chosen the size of the drug-containing adhesive so that the volume of substance included is the same for both cases. These dimensions may be further varied.

The development process of the presented patches contains several steps:

- choosing the appropriate geometry and dimensions;
- printing the capacitor's geometry to a copper layer through thermal transfer;
- one side lamination with a polyethylene foil before corrosion;
- removing the unnecessary copper through a corrosion procedure;
- external terminals attachment;

- sealing the coplanar capacitor through a second laminating process (any external substance should not be able to pass to the capacitor);
- attaching the substance layer to the backing with built-in capacitor (no air bubbles should be present between those two parts).

3. FUNCTIONAL SIMULATION

In order to predict the behavior of the patches, some simulations were performed using the COMSOL Multiphysics® software. Two modules of this software were used: Electrostatics and Species Transport in Porous Media.

The basic idea of the model was the fact that the electrical capacitance is influenced by the variation of the electrical permittivity of the environment in which the capacitor is placed in. The whole process of substance transport through the various layers of skin will determine a variation of the electrical permittivity and, subsequently, of the capacitance. The simulation results will show if this variation is significant enough to be measured.[13]

The model that we use for simulation is divided in three different domains: the backing with built-in capacitor, substance layer and a volume where the substance is transferred. Even if the skin is made by multiple sub layers and the thickness is different, for simulation we had considered a 1 cm compact domain with same properties.

The first process we had studied is the substance exchange process between patch and skin. In this case, phenomena like absorption, diffusion and dispersion were considered relevant. Considering the fact that the backing is impermeable, the transport phenomena in this domain were not computed.

To simplify the simulation, some assumptions have been made [1], [2], [3]:
- there are no chemical reaction phenomena throughout the entire process;
- there are no volatile components or gas absorption phenomena;
- the volume of the substance domain remains constant throughout the entire process;
- the absorption and transfer of any fraction of the delivered substance in the blood flux appears below the bottom boundary of the domain and is not considered by the simulation;
- there is no velocity of any medium considered due to the fact that the absorption process is driven only by the difference in the concentration [3]
- the temperature is constant and considered T=37ºC.

Another aspect of the simulation is to determine the capacitance, foreseeing the variation of the electrical relative permittivity in respect with the change of the concentration.

In this instance, all the domains are included in the simulation, but the variation of the electrical permittivity is considerable only in the patch and in the skin's layers. For the rest of components, the relative permittivity is considered constant or with an insignificant variation and a fixed value will be attributed.[13]

The initial simulation conditions were imposed with respect to: initial concentration of the substance, porosity of the materials, absorption, diffusion and dispersion coefficients and electrical permittivity of all materials involved.

The results of the simulations are focused on electrical potential distribution and the variation of the capacitance in respect with the concentration changes that result from mentioned phenomena.

The data obtained from simulation may be a bit different than the measured ones because of some of the material parameters that were used. This does not affect the comparison of the results because only the difference value of the capacitance is considered relevant.

A voltage of an amplitude of 5V was applied to the interior terminal, for the external one, a ground condition was imposed. Figure 2 and figure 3 show the electrical potential distribution for both models involved.

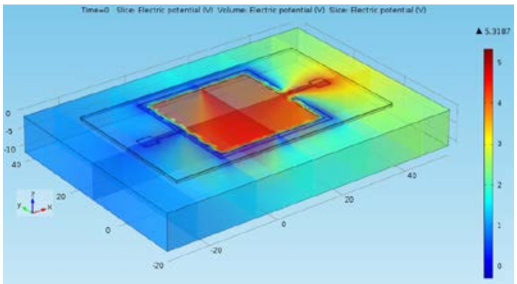

Fig. 2 The electric potential of the square shape model

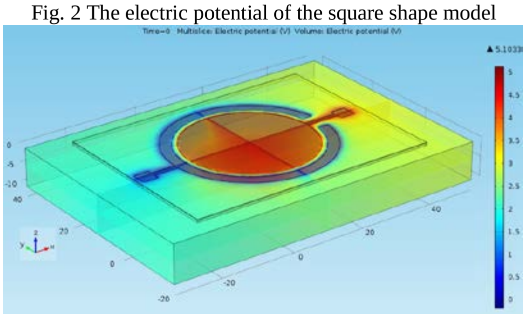

Fig. 3 The electric potential of the circular shape model

The capacitance can be computed starting from its definition $C=Q/U$. The electric potential difference is the line integral of the electrical field intensity and the electrical field intensity can be computed as a function of the electrical charge and the plate electrical charge density respectively. [10]

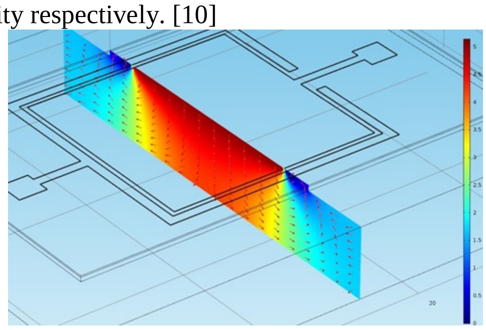

Fig. 4 Section view of the potential and electrical field lines of the square shape model

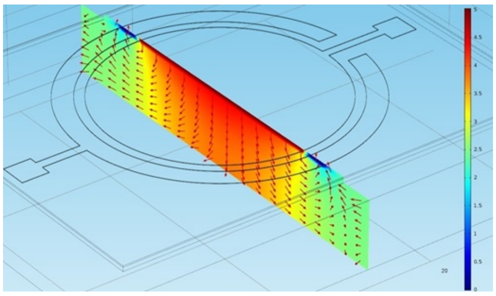

Fig. 5 Section view of the potential and electrical field lines of the circular shape model

In order to emphasize the variation of the capacitance in respect with the concentration of the solution, the simulation conditions were set to follow a 9 hour delivery process.

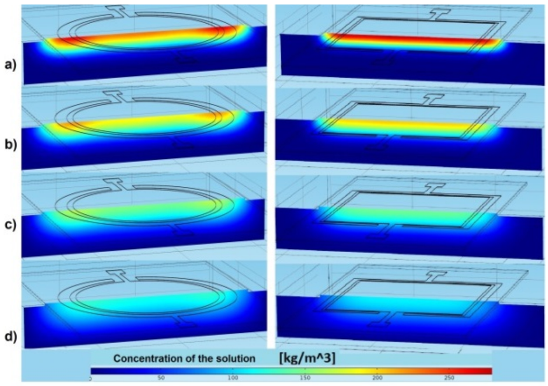

Fig. 6 The concentration of the released substance at different time intervals: a) the first hour; b) the third hour; c) the sixth hour; d) the ninth hour.

As it is shown in figure 6, the concentration of the solution varies in time, and with it, the electrical relative permittivity.

There are many parameters of the materials that can influence the behavior of the presented device: the porosity of the substance layer, the viscosity of the substance, the diffusion, absorption and dispersion coefficients, and many others. For this paper only the electrical relative permittivity variation is analyzed.

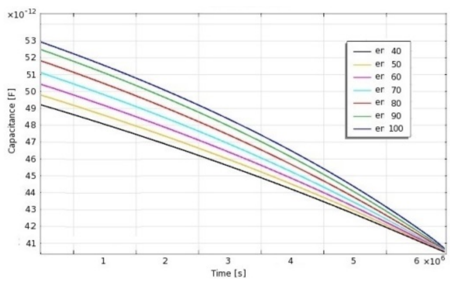

Fig. 7 The capacitance variation for different electrical relative permittivity of the substance

From figure 6 and 7, we can conclude that the capacitance decreases in time proportionally to the value of concentration. The absolute variation of the capacitance is around 10…12 pF, the difference was given by the different relative permittivity of the solutions.

4. EXPERIMENTAL RESULTS

Because the medical devices testing procedures are regulated by a strict legislation, the tests and the measurements that were performed were as close as possible to real situations.

The experimental setup contains: a Q-meter TESLA® BM560, a digital RLC-meter Protek® 9216A, two patches (one in circular and one in square shape), an insulating material support, two shielded wire connection, syringes and connecting tubes.

For the experiments, two working standards were imposed in order to obtain viable results. In order to decrease the experiments time, a reverse procedure was performed. Starting with an empty patch, a fixed volume of substance was injected into the substance layer until saturation occurs.

In the first situation, the measurements were performed using only the patch, without any absorption medium.

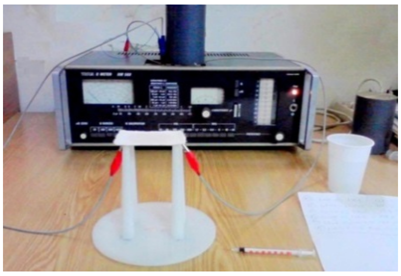

Fig. 8 The experimental setup used for first procedure

Three different substances were used: distillated water – $\varepsilon_r \approx 80$, alcohol diluted in water - $\varepsilon_r \approx 90$ and salt diluted in water $\varepsilon_r \approx 100$.

Each of these solutions was injected into the substance layer, the volume of one dose being 0.1ml.

In order to equally spread the substance in the cotton cloth, the injections were made each 30 seconds, the total amount of delivered substance being 1.5ml.

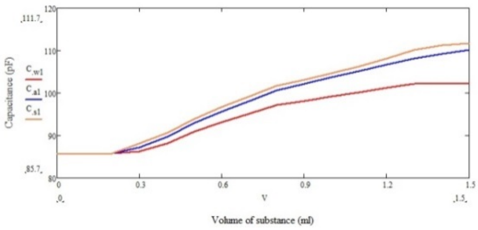

Fig. 9 The capacitance variation of the square shape patch without the external absorption medium

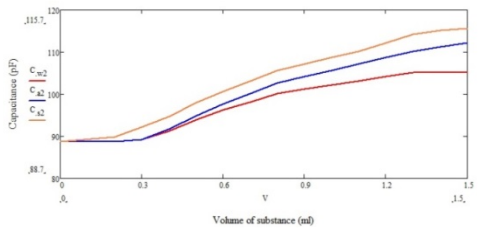

Fig. 10 The capacitance variation of the circular shape patch without the external absorption medium

In the previous figures, the capacitances are: C_{wi} for distilled water, C_{ai} for alcohol solution and C_{si} for salty solution.

The capacitance variation is in an expected interval, for the distilled water being around 10pF, for the alcoholic solution around 15pF and for the salty solution around 20pF. When the cotton cloth is saturated with solution, the capacitance becomes constant.

The second set of measurements was performed using an absorption porous medium, 30mm thick, attached to the patch. The presence of this environment allows us to create an anisotropic distribution of the substance under the patch.

Fig. 11 The experimental setup used for second procedure

The same substances were injected in the central part of the capacitor, between the the cotton cloth layer and the porous marerial. The dosage was the same as in the previous case.

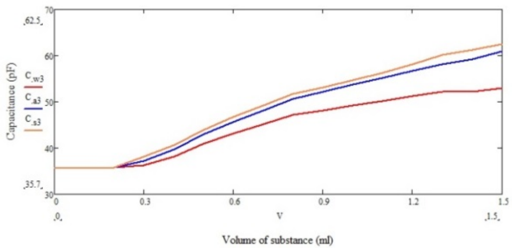

Fig. 12 The capacitance variation of the square shape patch with external absorption medium

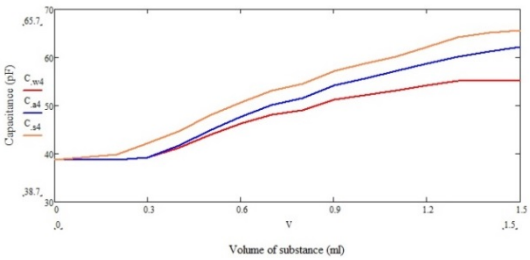

Fig. 13 The capacitance variation of the circular shape patch with external absorption medium

The presence of an absorption medium changes the capacitance difference value between saturated and empty substance layer. The reference value is also changed because of the difference of the electrical permitivity between air and the porous material.

From the graphical representation of the capacitance variation we can say that the values are bigger with 5…10 pF from the previous procedure, but the variation characteristics have mainly the same shape.

5. CONCLUSIONS

This paper presents the comparative results obtained from functional simulation and practical measurements made for two types of patches filled with a substance. The delivery process of the substance in a certain medium is monitored with a capacitive method.

In order to decrease the experiments time, a reverse procedure was performed. Starting with an empty patch, a fixed volume of substance was injected into the substance layer until saturation occurs. Even though in the real situation the substance goes out from the patch, the results allow us to say that the method presented is plausible.

The values obtained from the two tests were relatively similar with the ones from simulation. The capacitance varies around 10…20 pF, values which are relatively small, but measurable with some dedicated electronic circuits. Although, the measurement of small capacity (in the order of pF), may be affected by some external factors, such as frequency, temperature, humidity, atmospheric pressure, etc. laboratory experiments have given optimum conditions for minimizing the influence of those perturbing factors.

The presented monitoring method is not unique, but it is both simple and inexpensive, any limitations that may occur are related to the properties of materials and substances used.

The future work will include a capacitive matrix inserted in the patch, for better measurements of the anisotropic medium.

REFERENCES

1. BEAR J., “Introduction to Modeling of Transport Phenomena in Porous Media”, Springer, 1991, ISBN 978-0792311065
2. BEAR J., “Dynamics of Fluids in Porous Media”, American Elsevier Publishing Company, 1978, ISBN 798-0-486- 65675-5.
3. BIRD B.R., et al., “Transport Phenomena - 2nd edition”, John Wiley & Sons, 2002, ISBN 0-471-41077-2
4. CARPI F.,et al., “Dielectric Elastomers as Electromechanical Transducers”, Elsevier Science, 2008, ISBN 978-0080474885
5. CHEREPANOV D.A., et al., “Low Dielectric Permittivity of Water at the Membrane Interface: Effect on the Energy Coupling Mechanism in Biological Membranes”, Biophysical Journal, 85, pp. 1307–1316, 2003.
6. DEMORI M., et al., “A Microfluidic Capacitance Sensor for the Fluid Discrimination and Characterization”, Procedia Engineering, no.5, 2010, pp. 408-411
7. DEMORI M., et al., “A capacitive sensor system for the analysis of two-phase flows of the oil and conductive water”, Sensors and Actuators A: Physical, no. 163, 2010, pp.172-179
8. GROSSE C, et al., “Calculation of the Static Permittivity of Suspensions from the Stored Energy”, Journal of Colloid and Interface Science, 193, pp. 178-182, 1997.
9. RANDALE V., HOLLINGER M., “Drug Delivery Systems” Second Edition, CRC Press, 2004, ISBN 0-8493-1433-X.
10. SORA C., “Bazele Electrotehnicii”, Editura Didactica si Petagogica, Bucuresti 1982.
11. TESCHKE O., et al., “Interfacial Water Dielectric-Permittivity-Profile Measurement Using Atomic Force Microscopy”, Physical Review E, 64, 2001.
12. ȚEBREAN B, et al., “Modelling of a capsule for controlled slow delivery, monitored via a capacitive method”, Acta Electrotehnica, vol. 53, nr. 4, 2012, pp. 323, ISSN 1841-3323
13. ȚEBREAN B, et al., “Modelling of the Coplanar Capacitors for Dermal or Transdermal Drug Delivery System Monitoring,

Proceedings of the Romanian Academy, Series A, volume 14, nr. 2/2013, pp.134-143, ISSN: 1454-9069
14. ȚEBREAN B, et al., Capacitive Monitoring of a Tubular Layered Substance Delivery System, IFMBE Proceedings, Vol. 44, 2014, pp 197-202 International Conference on Advancements of Medicine and Health Care through Technology MediTech, Cluj-Napoca, Romania.
15. VASQUEZ J. L., “The Porous Medium Equation- Mathematical Theory”, Oxford University Press, 2006, ISBN: 978-0198569039.
16. WANG P., ANDERCO A., “Computation of Dielectric Constants of Solvent Mixtures and Electrolyte Solution”, Fluid Phase Equilibria, 186, pp. 103-122, 2001.
17. WARSI Z.U.A, “Fluid Dynamics: Theoretical and Computational Approaches”, Third Edition, Taylor and Francis, 2005, ISBN-13: 978-0849333972.
18. WEI B., YANGA J., et al., “Design and numerical simulation of a humidity sensor based on CMOS fabrication technology”, Physics Procedia, 18, pp. 31–39, 2001.
19. YAWEN LI, “In vivo release from a drug delivery MEMS device”, Journal of Controlled Release, 100, pp. 212-219, 2004.

Bogdan ȚEBREAN
Septimiu CRIȘAN
Valentin D. ZAHARIA
Titus E. CRIȘAN

Electrical Engineering and Measurements Department
Faculty of Electrical Engineering
Technical University of Cluj-Napoca
Str. Memorandumului nr. 28, 400114 Cluj-Napoca