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MODELLING OF THE COPLANAR CAPACITORS FOR DERMAL OR TRANSDERMAL DRUG DELIVERY SYSTEM MONITORING

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The aim of this paper is to investigate the possibility of using coplanar capacitors in monitoring dermal and transdermal drug delivery systems. One of the main problems concerning those systems is the real-time monitoring of the quantity of the active component transfered into the main bloodstream or to the tissue of interest. The coplanar capacitor being a clasical solution for humidity measurements, it appears reasonable to try and sense the variation of the concentration of the active substance as it passes through the various layers of skin. Different practical possible situations are analyzed, starting with constructive issues and continuing with the simulation of the drug delivery system in different imposed situation. The modeling was performed using a finite element method and was based on the energetic approach for capacitance and on the equation describing the transport of the solutes in variable saturated porous media respectively. Different practical possible situations were analyzed, starting with constructive issues and continuing with the simulation of the drug delivery system in different imposed situations.

Key words: dermal or transdermal drug delivery systems, coplanar capacitors, capacitive sensors, biomedical transducers, biomedical monitoring.

1. INTRODUCTION

Drug dermal delivery is a well known process and is mainly used for either local treatment of localised skin diseases or near skin muscle/tissue disorders. Transdermal delivery systems are designed to deliver the drug from a source, placed outside the body, to the bloodstream, penetrating through skin's various layers. Even if these devices are wildly used and many theoretical approaches of the phenomenon ware stated, due to the fact that the penetration of the skin is a complex process, it is difficult to predict precisely the amount of drug that is really delivered to the bloodstream at any precise moment or over a given time [1].

This paper presents a model of a medicated adhesive patch which uses a capacitive transducer to monitor the amount of substance delivered through the skin. Different possible practical situations will be analyzed, starting with constructive issues and continuing with the simulation of the drug delivery system in various imposed situations. The main phenomenon to be taken into account in monitoring the absorption process is the variation of the capacity of the transducer due to the variation of the relative electrical permittivity of the body part.

2. MODELLING CONDITION

2.1. Device configuration

Two types of drug delivery systems were studied, the main difference being the shape of the patch and of the coplanar capacitor; the first configuration is a cylindrical one and the other one is parallelepipedal with a square base, as shown in Fig. 1:

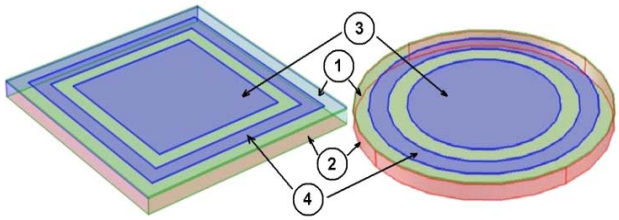

Fig. 1 – The main components of drug delivery system.

The parts of the experimental models are similar in both cases: 1) backing with built-in capacitor, 2) drug-containing adhesive, 3) coplanar capacitor voltage armature and 4) coplanar capacitor ground.

The backing with built-in capacitor is made of impermeable polyethylene. The capacitors are laminated into two layers, the total thickness of the transducer being 0.2mm.

The capacitor plates, voltage armature and ground, are made of copper, with a thickness of 0.1mm.

The interior plate area is in both cases 400mm^2, with the following dimensions:

– for the parallelepipedal one: the interior edge – 20mm, the exterior edge – 24mm, spaced at 2mm;

– for the cylindrical one: the interior radius – 11mm, the exterior radius – 14mm, spaced at 2mm.

The volume of the stored drug 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. Given the dimensions of the capacitor, the dimensions for the patches are 17mm radius for the cylindrical one and 30 mm^2 square for the parallelepipedal one with a thickness of 2mm; thus the volume is 1800mm^3. These dimensions may be further varied, but this hypothesis will be a part of a future study.

2.2. General modelling condition

The modelling was performed using the COMSOL Multiphysics® software, with two modules: Electrostatics and Species Transport in Porous Media.

The reason why such an approach is possible is the fact that the electrical capacity of any capacitor is influenced by the variation of the electrical permittivity of the environment the capacitor is placed in. The whole process of drug transport through the various layers of skin will determine a variation of the electrical permittivity and, subsequently, of the capacity. The simulation results will show if this variation is significant enough to be measured.

According to [2], the transport phenomena refer to the fact that one or more extensive quantities (i.e. quantities that are additive over volumes, with mass, momentum and energy as examples) are transported through the solid and/or fluid phases that together occupy a porous medium domain. To solve a problem in such a domain means to determine the spatial and temporal distribution of state variables (e.g. velocity, mass, density, pressure, concentration of a solute).

Generally, what is called a transport phenomenon for a drug delivery system may include one or more of the fallowing: *absorption* (the movement of a drug till he reach the blood stream), *dispersion* (the spreading of mass, as species travel through a porous medium), *diffusion* (mixing or mass transport without requiring bulk motion), *chemical reaction* (biodegradation, radioactive decay, transformation to tracked products, temperature and pressure dependent functions, exothermic reactions, and endothermic reactions) and *advection* (the movement of a solute with the bulk fluid velocity defined as volume flow rates per unit cross section of the medium) [2, 3].

The process we studied was considered to be a typical absorption process, thus the following assumptions have been made:

– there are no chemical reaction phenomena throughout the entire process;

– there are no volatile components or gas absorption phenomena throughout the entire process;

– the diffusion phenomenon, although present, were considered to be of a significantly lower importance compared to the absorption phenomenon, but it was included in the model (D_e=7·10^{-14} m^2/s);

– there is no dispersion present;

– the absorption and transfer of any fraction of the delivered drug 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 above assumptions are further more by the essential quasi-static nature of the phenomenon, this being also the reason for the adopted process time of 9 hours.

Theoretically, 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 function of the electrical charge and the armature electrical charge density respectively [4].

Thus the electrical capacitance of an electrical field tube between two conductive surfaces can be written as:

$$\frac{1}{C}=\frac{V_1-V_2}{Q}=\frac{\int_1^2 \overline{E}\cdot\overline{\mathrm{d}l}}{\int_{\Delta S}\overline{D}\cdot\overline{\mathrm{d}s}}, \tag{1}$$

where 1 and 2 are the conductive surfaces at the ends of the field tube, l_{12} is a field line between surface 1 and 2 and ΔS is a section of the field tube.

Equation (1) is useful for simple systems with a certain symmetry, the essential condition consisting of a known function $\Delta S=f(l)$. For complex systems (e.g. systems where the end effects cannot be disregarded), the integrals above must be numerically computed. However, for a more comprehensive approach for numerical methods it is preferable to use an energetic approach.

For any given geometry, a working volume (physical volume) is defined and the capacitance is computed for the respective volume. If we consider a system with n armatures, at least one of the armatures must be grounded and the global capacitance is computed using the superposition method. For this system the capacitance is computed according to equation (2):

$$C_{ij}=\frac{1}{V_iV_j}\int_{\Omega}W_e\,\mathrm{d}\Omega-\frac{1}{2}\left(\frac{V_i}{V_j}C_{ii}+\frac{V_j}{V_i}C_{jj}\right), \tag{2}$$

where V_i is the electrical potential of the i element, W_e is the energy and Ω is the integration volume.[5] The particular structure of the coplanar capacitor from Fig.1 either in the circular or square form, cannot be considered as a simple two armature system due to its form, so we consider the approach presented above as necessary. For the simulations, the dimensions of the working volume were given by the capacitor as well as by the real skin layers dimensions.

From a medical point of view the dermal and transdermal drug delivery systems are considered noninvasive treatments. The base of such assumption is the fact that the drug is absorbed by the organism through the skin due only to the concentration difference of the substance and the porosity of the derma. This made us to approach the problem considering the variable saturated porous media situation. This model is defined for the case when a porous media (the drug-containing adhesive) is primarily filled with liquid and during the delivery process is replaced by air. The general case equation describing the transport phenomena, derivates from Richard's equations [1, 6, 7]:

$$\frac{\partial}{\partial t}(fc_i)+\frac{\partial}{\partial t}(\rho_b c_{a,i})+\frac{\partial}{\partial t}(\alpha_v c_{g,i})=\nabla[(D_{D,i}+D_{e,i})\nabla c_i]+Q_i+F, \tag{3}$$

where: c_i – the concentration of species i in the liquid (mass per liquid volume); c_a – the amount adsorbed to solid particles (mass per dry unit weight of the solid); c_g – the concentration in gas phase (mass per volume gas); f – the liquid volume fraction; ρ_P – the solid phase density; ρ_b – the bulk density; α_v – the resulting gas volume fraction; D_D – the dispersion coefficients; D_e – the effective diffusion coefficients; $c_{p,i}$ – the solute mass of species i absorbed to solids; $c_{g,i}$ – the solute mass of species i dissolved in the gas-phase; Q_i – the reaction rate; F_i – the fluid source (species i source).

Considering the previous assumptions and expanding the div(D·grad(c_i)) term, we obtain:

$$\frac{\partial}{\partial t}(fc_i)+\frac{\partial}{\partial t}(\rho_b c_{a,i})=(f+\rho_b\frac{\partial c_{p,i}}{\partial c_i})\frac{\partial c_i}{\partial t}-\rho_p c_{a,i}\frac{\partial f_s}{\partial t}, \tag{4}$$

where the absorption follows the Langmuir absorption equation for one species [6]:

$$\frac{\partial c_a}{\partial c} = \frac{k_L A}{(1 + k_L c)^2}, \tag{5}$$

where: k_L is the Langmuir constant and A is the maximum absorption.

The relative permittivity shows variations both because of the concentration of the transported species and because of the type of the species. Due to the specifics of the drug manufacturing field, there are little or no resources giving the relative permittivity of various drugs used for dermal patches. For the purpose of the simulation we have considered a variation of the relative permittivity with the drug concentration for values close to the water absorption in tissues.

The major concern was to offer some predictable solutions for determining the concentration of delivered substance. For that reason, the simulation solve simultaneous the two problems: the transport phenomena and the electrostatic issues. The initial condition, the variables and the solving restriction will be performed in two aspects, imposed by the software ability to solve the problem: domain and boundary level. The boundary level can replace the exterior of the domain when the modelling domain is unbounded or too large for successful meshing and analysis.

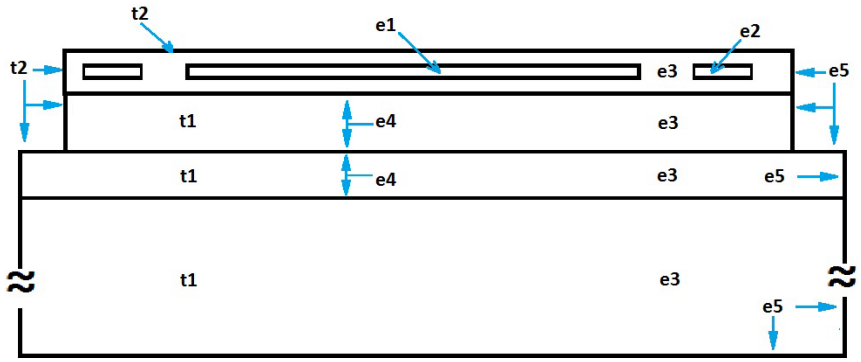

Fig. 2 – Simple sketch of the computational domain.

The first, the transport of the species in porous media, can predict how the drug passes through the porous layers represented by the patch and the skin layers.

Because the backing of the patch is considered impermeable and the capacitor's armatures are laminated in it, these elements will not be included in the transport phenomena analysis. So for the rest of the domains the condition is *mobile fluid/immobile solid* (t1 Fig. 2) (in respect with equation (4)) for the porous domains (drug-containing adhesive, epidermis, dermis and hypodermis), exception being the exterior boundary of the domains where we have to impose *no flow/no flux* condition for species (t2 Fig. 2), this allow us to presume that there is no other substance flux of flow components that may influence the delivery process, beside the drug from the patch.

The second 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. These values will be computed with the equation (6). For the rest of domains, the relative permittivity is considered constant or with an insignificant variation and a fixed value will be attributed.

The domain conditions are: *electric potential,* $V=V_0$ (e1 Fig. 2), for the capacitor's voltage armature, *zero voltage,* $V=0$ (e2 Fig. 2), for the capacitor's ground armature and *charge conservation,* $\vec{E} = -\nabla V$ (e3 Fig. 2), for the rest of the domains.

The boundary conditions are similar with the domain condition for the armatures boundaries and *continuity* (e4 Fig. 2) for all the remaining interior boundaries, (no other condition overwrite the interior boundary condition, so the software ensures continuity in the field variables across the interior boundaries).

For the exterior boundaries the condition is *zero charge,* $-nD = 0$ (e5 Fig. 2), for the exterior ones, where n number of charge carriers and D is the electric displacement field.

3. MODELLING RESULTS

The simulations were performed using a FEM dedicated software both for the electrostatic and the transport situations. The capacity was computed in three successive situations, each step building on the previous one in order to obtain a closer model to the actual situation:

a) Transducer – the coplanar capacitor embedded in backing;

b) Drug delivery system – the backing with built-in capacitor and drug-containing adhesive;

c) Drug delivery system with a release environment.

It is important to mention that when the relative permittivity is constant or varies uniformly in the model domain, we have used only the "Electrostatic" approach and when the mixture of substances affecting the relative permittivity and its distribution is anisotropic, the mass transport approach is needed to find the concentration of chemical species in various environments.

3.1. Coplanar capacitor embedded in the backing

The outermost layer of a transdermal drug delivery system is the backing. The first analyzed situation is of a coplanar capacitor laminated in a polyethylene backing. The physical properties of this material allow it to prevent evaporation or loss of the drug, while also protecting the drug from the adhesive on the exterior environment and, in this particular case, preventing the oxidation of the capacitor plates and the undesired electric contact between the voltage armature and ground [1].

The initial simulation conditions are: the relative permittivity of the backing – $\varepsilon_{r\ backing} = 2.3$ and the voltage applied to the armature is $V_0 = 5$V. The mesh that is used in this case is a customized one, because the difference between the size of the lateral boundaries and the face of the parallelepiped or of the cylinder was significant. To solve this issue, we have to choose two different triangular mesh sizes for the boundaries and faces, as it is shown in Fig. 3. A further refining of this mesh was considered ineffective because the differences between successive (from the mesh point of view) computed capacitances are lower than 10^{-15}F and does not justify the increase in computing time.

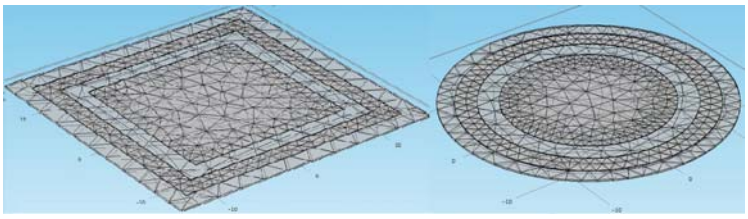

Fig. 3 – The representation of the mesh for the coplanar capacitors.

As shown in simulation results, presented in Fig. 4 and Fig. 5, the capacitance of the parallelepipedal sensor is 0.88 pF and of the cylindrical one is 0.32 pF. These values are relatively small, but they are expected to increase when a dielectric layer, with a bigger relative permittivity than the air, will be attached under it. From a medical point of view, the patch must provide a uniform delivery, maintaining a constant flux and avoiding an over dosage. The behavior of the drug-containing adhesive, in electrical terms, is a variable dielectric medium, with a consistent variation of relative permittivity (in our case $\varepsilon_r \approx 2.65 \ldots 80$).

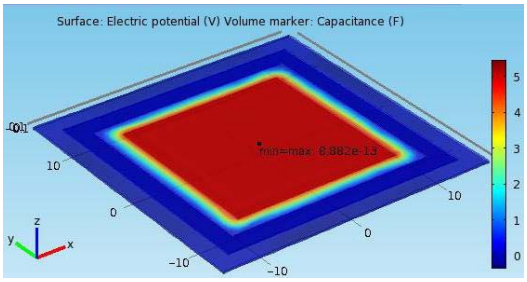

Fig. 4 – The electric potential and the capacitance of parallelepipedical capacitor.

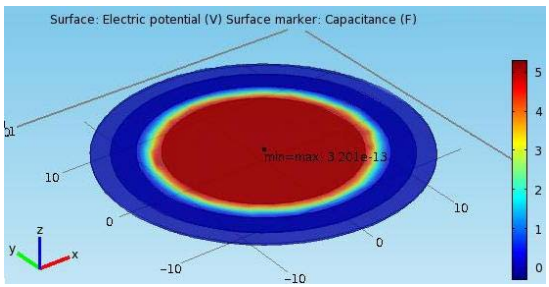

Fig. 5 – The electric potential and the capacitance of cylindrical capacitor.

For this model, the material that we choose for the drug-containing adhesive is EVA 12% VA (ethylene vinyl acetate with a concentration of 12% vinyl acetate). This material has a low water absorption coefficient, under 0.05%, and a higher tensile strength and permeability than commonly used EVA with a higher concentration of vinyl acetate, 25% or 33%. The relative permittivity of this material is $\varepsilon_{r\,EVA} = 2.65$ [8].

The simulations of this particular case were made in several distinct situations, depending on the concentration of the drug present in the patch.

The first case is with an empty patch, the relative permittivity being constant throughout the material. The same mesh was maintained for the numeric computations regarding the capacitive transducer while for the adhesive domain we have chosen a tetrahedral mesh in respect with the backing meshed surface (Fig. 6).

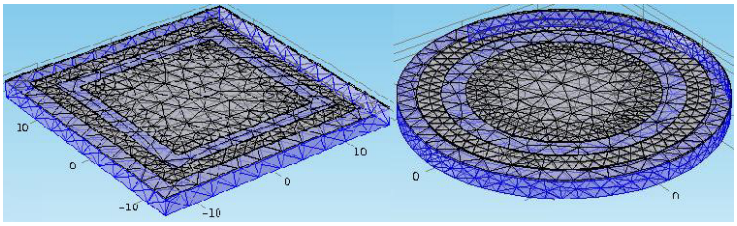

Fig. 6 – The representation of the mesh for the backing with built-in capacitor and drug-containing adhesive.

The results presented in Fig. 7 and Fig. 8 show that the presence of the 2mm dielectric layer under the capacitors increases the capacitance of parallelepipedal capacitor at 1.99pF and of the cylindrical one at 1.21pF. It is expected that in the presence of a higher relative permittivity drug in the patch, the capacitance would increase significantly.

The second case studied for this configuration presents the variation of the capacitance when the relative permittivity of the drug-containing adhesive varies from the $\varepsilon_{r\,drug} = 80$ value corresponding to a drug mixture with a high concentration of distillated water, to $\varepsilon_{r\,drug} = 2.65$ – the relative permittivity of an empty adhesive.

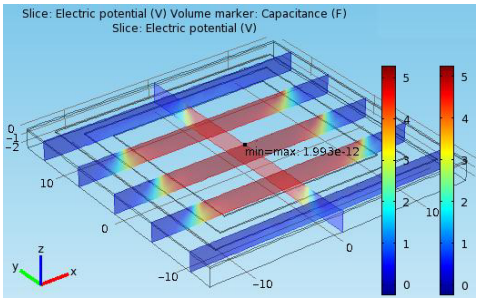

Fig. 7 – The electric potential and the capacitance of the parallelepipedical backing with build-in capacitor and empty patch.

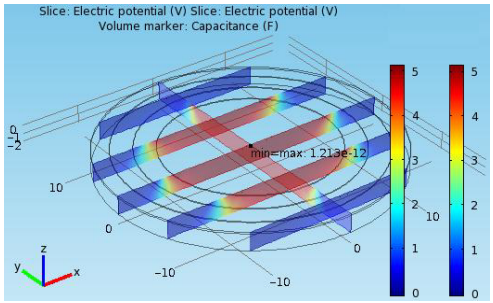

Fig. 8 – The electric potential and the capacitance of the cylindrical backing with build-in capacitor and empty patch.

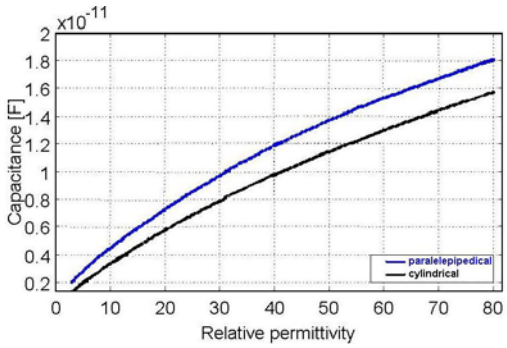

Fig. 9 – The dependence of the capacitance in function of relative permittivity of the drug-containing adhesive.

This variation can be assimilated even with an initial value of a full patch with different types of drugs or a constant drain of the substance from the drug-containing adhesive. The results are presented in Fig. 9.

The value obtained with the parallelepipedal capacitor is always bigger than the cylindrical one, the maximum values being around 18 pF and 16 pF, respectively. As stated above, even if the capacitance values are rather small they are perfectly measurable – so that further practical implementation of the device is considered possible at this stage.

3.2. Backing with built-in capacitor and drug-containing adhesive

The most important part of the study is the behavior of the drug delivery system when attached to a release environment. In this case, the problem must be individually analyzed for two specific situations: dermal and transdermal delivery.

The dermal delivery systems must deliver the substance to a local part of the skin, especially in the superior layer, without a deep penetration of the drug into the skin substructure. Transdermal delivery systems are designed to deliver the drug to the bloodstream, penetrating through skin's various layers.

It is known from previous studies that most of the relative permittivity values of the human skin are within the range of $\varepsilon_{r\ skin} = 20\ldots50$. [9] The values are different depending on the body region and, most importantly, on the water concentration in the tissue layers. For this simulation the permittivity was considered to vary within the whole interval stated above due to the presence of various drugs absorbed by the skin. The thickness of the skin's layers was chosen to be closely related to the arm or the hip tissue scale, as these parts of the body are the most often used for this kind of applications.

The models were designed for two distinct situations:

– the dermal delivery system was built using an active layer (with variation of relative permittivity), presumed as 1mm thick and containing the epidermis and dermis, and an additional passive layer (no permittivity variation being involved), 10mm thick and representing a reasonable value for the hypodermis;

– the transdermal delivery system – both mentioned layers are considered active, the relative permittivity varying in respect with the amount of substance absorbed.

For both situations, the area of interest was considered to be cylindrical, with a 30mm radius base. The mesh for the skin domains, represented in Fig. 10, was chosen to be tetrahedral, the size and the growth rate of the elements being maintained the same as at for the backing with built-in capacitor and drug-containing adhesive models.

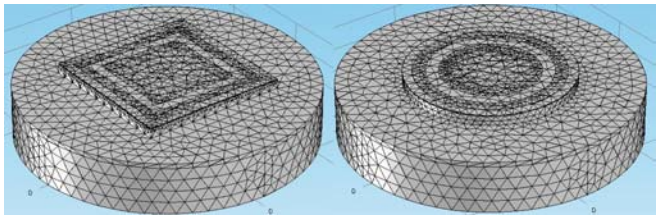

Fig. 10 – The representation of the mesh for the dermal and transdermal drug delivery system models.

Even if it is possible to modify the mesh so as to consist of parallelepipedal elements in order to reduce the computations, we have maintained the same mesh type as above for the benefit of consistency between the various steps of the models.

a) *The Dermal Drug Delivery System Model*. For the dermal delivery system the relative permittivity of the drug-containing adhesive will vary within $\varepsilon_{rdrug} = 80\ldots2.65$, the dermal layer relative permittivity within $\varepsilon_{rderm} = 20\ldots50$, and the hypodermal layer relative permittivity will be maintained constant at $\varepsilon_{rhypo} = 50$. The simulation results are shown in Fig. 11 and Fig. 12:

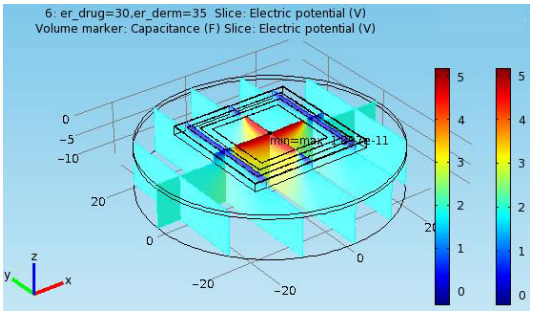

Fig. 11 – The electric potential and the capacitance of the parallelepipedical dermal drug delivery system.

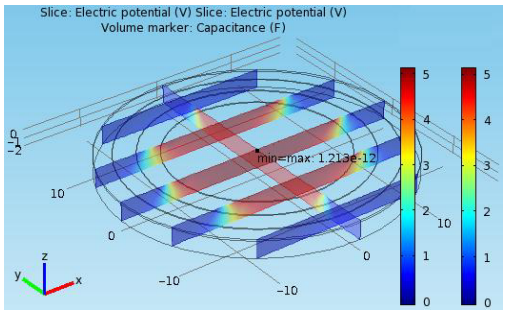

Fig. 12 – The electric potential and the capacitance of the cylindrical dermal drug delivery system.

The results show that the variation of the capacitance is consistent, $\Delta C_{par} \approx 35$ pF for the parallelepipedal capacitor and $\Delta C_{cyl} \approx 20$ pF for the cylindrical one. These differences between values can predict various levels of drug presence in the patch.

Fig. 13 and 14 present the capacitance variation with respect to the variations of the relative permittivity of the patch and of the skin layers. Using the same simulation conditions, a variation of the hypodermal layer relative permittivity, $\varepsilon_{r\,hypo} = 50\ldots70$, will produce a very small change of the capacitance, $\Delta C \approx 0.01\ldots0.05$ pF, this value being insignificant for the measurement result.

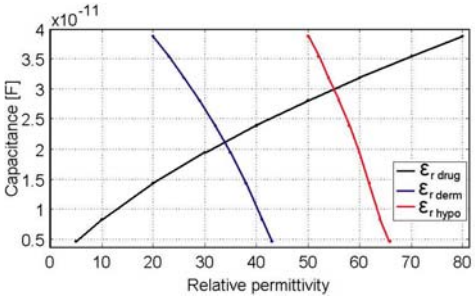

Fig. 13 – The dependence of the capacitance for the parallelepipedical drug delivery system.

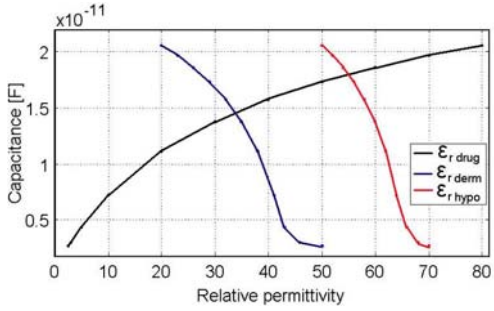

Fig. 14 – The dependence of the capacitance for the cylindrical dermal drug delivery system.

b) *The Transdermal Drug Delivery System Model*. For the transdermal drug delivery system the simulation conditions were changed. The variation of the relative permittivity of all model's domains was obtained using an approximate relation closely related with the drug concentration from the layers.

The initial conditions imposed for the solute transport model were different for each domain, the most important values being the saturation of the environment and the absorption coefficient. For the patch, the saturation must be high and absorption under 1%. For the dermal layer, the saturation must have low values; for that reason, the imposed condition of the absorption was that 80% of the drug must be transferred from the patch to this layer. The hypodermic layer was considered at a medium saturation and the absorption was set to 30% of the volume that passes through the dermal layer.

The correlation between the relative permittivity and the concentration of the substance was considered to behave according to the following relation:

$$\varepsilon(c) = \frac{\varepsilon_{max}}{1 + (\varepsilon_{max} / \varepsilon_{min} - 1) \cdot e^{-z/k}}, \tag{6}$$

where: ε_{max} is the relative permittivity of the drug-containing adhesive at the beginning of the process, ε_{min} is the relative permittivity of the drug-containing adhesive fully voided of the active substance, z and k represent the rate of diffusion and absorption correlation coefficients between the source and destination layers. The $-z/k$ coefficient is function of both the drug and its concentration. For the purpose of the simulation and based on the few data available on substances, we have chosen an approximate function $z/k = 1.5 \cdot \ln(c) + 1.2$. These coefficients are also close related to the penetration distance of the drug into the skin layers. The values for the minimum and maximum relative permittivity can be measured separately using a known substrate. The choice of such dependence between concentration and permittivity was made as an extension of previous works [10, 11, 12, 13] regarding the species transport through thin membranes. We consider this approach valid because of the layered structure of the patch-skin configuration

The maximum and minimum values of the relative permittivity were chosen close to the values previously used. For the drug-containing adhesive the relative permittivity was within the range of $\varepsilon_{r\,drug} = 80\ldots2.65$, the dermal layer relative permittivity within the range of $\varepsilon_{r\,derm} = 20\ldots50$ and the hypodermal layer relative permittivity within the range of $\varepsilon_{r\,hypo} = 50\ldots70$.

The initial concentration of the drug present in the patch was considered 900 kg/m^3 and 0.001 kg/m^3 in the skin layers. The bulk density of the skin layers was considered 1071 kg/m^3 for the dermal layer, 950 kg/m^3 for the hypodermal layer and 960 kg/m^3 for the drug-containing adhesive. The liquid volume fraction was considerate 0.7 in the adhesive and 0.3 in skin layers.

The period for the delivery process was set to 9 hours, the necessary time to drain more than 50% from the drug-containing adhesive.

The simulation results are shown in Fig. 15 and Fig. 16, the variation of the resulted capacitance being $\Delta C \approx 8$ pF.

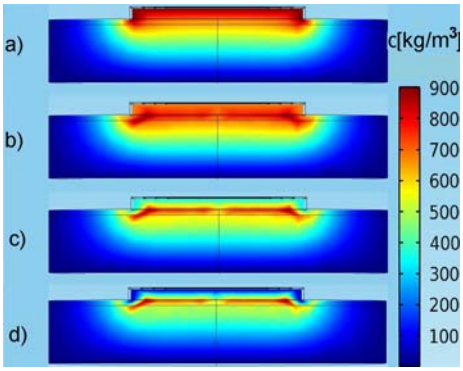

Fig. 15 – The concentration of the released drug for different time intervals: a) the first hour; b) the third hour; c) the sixth hour; d) the ninth hour.

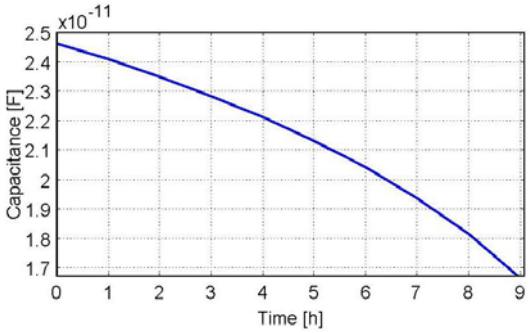

Fig. 16 – The capacitance variation in time.

Even if apparently the variations of capacitance obtained are relatively small (10^{-11}F order), those are values perfectly measurable, avoiding all interferences and there already are several common applications: finger-print readers, certain touch-screen devices, capacitive humidity sensors.

4. CONCLUSIONS

The simulations presented in this paper refer to the particular case of a dermal or transdermal drug delivery system that uses a capacitor sensor to monitor the drug concentration. The aim was not to fully analyze the dermal/transdermal absorption process, but to obtain a device that can be used to monitor this process. The delivery process is only monitored and not driven by any external electrical or magnetic stimuli.

To improve the response of the capacitive transducer, it is possible to consider working in alternative current with different amplitude and frequency conditions.

The presented method of monitoring the drug concentration is not considered a unique solution for this kind of application. It comes as an additional method that can supplement the current practical alternatives.

The study of the above presented phenomena for longer periods of time (e.g. till all the active substance is delivered) is planned to be a subject of subsequent studies.

Last but not least, from the measurement point of view, the values predicted through the simulations are measurable using rather classical methods, so that we have chosen not to dwell on this topic at this time. - 8pF is measurable with an adequate precision (e.g. using ultra-low power MSP 430 from Texas Instruments).

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