Promoting Medication Adherence by Redesigning Medical Blisters - The Smartblister approach

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***Abstract*—It is widely known and accepted in the medical field that accurate medication treatment is crucial for patient's outcome, especially amongst patients with chronic diseases. According to World Health Organization (WHO), low level of medication adherence leads to increased mortality rate and immense medical costs. Important research efforts have been dedicated to finding an objective way to assess and increase the level of medication adherence. The aim of the Smart-Blister project is to study, design and develop a novel methodology, which uses electronic circuits embedded in the blisters to detect the exact time that a pill has been removed. The proposed methodology consists of (a) a smart blister with a passive electronic circuit directly screen printed onto the blister or onto a self-adhesive substrate (smart-label approach) using a conductive ink, and (b) a small electronic device, that activates the blister and communicates with a central information cloud computing system. The proposed design can be easily adopted and allow for potentially scalable production of low-cost smart blisters. Moreover, the activation device is reusable, can be used with various blisters and it is expected to be of low-cost.**

Keywords—medical compliance, medication adherence, smart label, smart blister

I. Introduction

World Health Organization (WHO) has conducted studies, which determine that the level of medication adherence amongst patients with chronic diseases is around only 50% in the developed countries [1]. This is considered as an important health issue because lack of medical compliance could have a strong impact on citizens' health and could lead to enormous medical costs and increased mortality rates [2][3][4].

An accurate medical treatment is crucial for the patient's outcome, thus it is very important to take steps towards the increase of the level of medication adherence. Medication adherence level can be assessed through subjective [5] or objective methods [6][7]. The scientific community has made important efforts in order to find objective ways to assess and increase the level of medication adherence, using:

- Measurements of medicine in blood and its metabolic concentration [8].
- Prescription and medication sales data analysis [9][10][11].
- Electronic medication packaging [12][13][14].
- Smart blisters, devices that typically employ RFID technology and electronic circuits embedded in the blisters [15][16][17] to detect the time that a pill has been removed.

Smart blisters are of high cost and have the disadvantage of non-real time transmission. By embedding five-layer printed circuits on the back side of the blister [18], the problem of non-real time transmission of large amount of data can be addressed but the resulting device is of high cost and cannot be implemented in mass product.

The Smart-Blister project aimed to study, design and develop a novel methodology which addresses the challenges that smart blister methods face to date. The proposed methodology is based on a low-cost technology that can be easily adopted and realised in mass production, thus increasing the level of medication adherence and preventing from undesirable pharmaceutical usage and/or spoilage.

II. System Description

The proposed system presented in this manuscript consists of (a) a smart blister that integrates a passive electronic circuit, and (b) a small electronic device (the actuator), which activates the blister and communicates with a central information cloud computing system (Figure 1). The passive electronic circuit which detects the removal of a pill is printed on the film that is attached on the back of each blister. Specifically, the circuitry is printed directly onto the blister surface or printed onto a self-adhesive paper substrate and further transferred to the blister (smart-label approach). This circuit has contacts on the side of the blister in order to easily attach to them a small activation and communication device in the shape of a small latch. This device "monitors" the printed circuit, detects periodically the status of each pill, whether it is in place or removed and it communicates wirelessly with the Central Information System. Additionally, the device can handle optical and acoustical signals in order to inform the patient during his treatment.

Each device is activated by a pharmacist, who also registers the corresponding patient. During the registration, the pharmacist also registers the dosage and the frequency of the medication, along with the duration of the treatment as prescribed by the patient's doctor.

The doctor, with the patient's consent, is able to monitor the patient's medication adherence via the Central Information System and adjust the treatment accordingly.

The patient and/or his/her caregiver is also able to monitor the patient's medication adherence via the Central Information System. Additionally, if the patient does not adhere to the registered treatment, e.g. misses a pill, the caregiver can be notified by the Central Information System in real time.

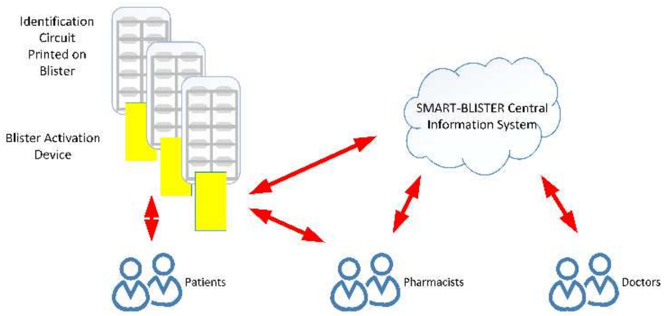

Figure 1. General Architecture of Smart Blister.

III. SMART BLISTER EMBEDDED CIRCUIT

The smart blister circuits are integrated on the back side of the blisters and they have the decisive role to recognize at any time the number of the remaining pills of the blister. These circuits meet the following criteria:

- They are passive circuits, powered by small activation devices. Their electrical connection is made with a special contact plug of high mechanical strength.

- The integration of the circuit on the blister has been done in such a way, that no short circuit occurs between the circuit and the foil that seals the blister.

During the design process of the passive electronic circuit that is integrated on the back of the blisters, two different approaches were studied:

a) The analog approach, where the small activation device measures the analog resistance of the loops of the printed circuit (Figure 2). In this approach the circuit would be produced by a combination of conductive and graphite inks.

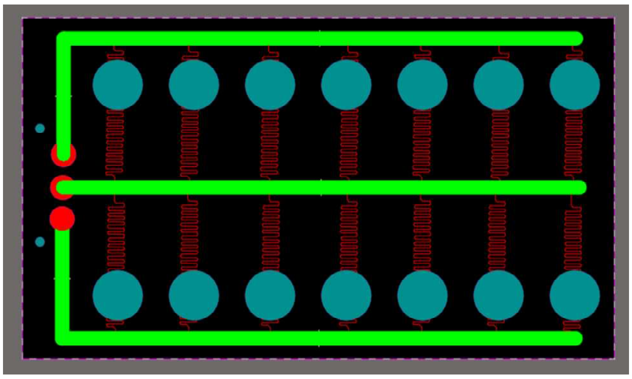

Figure 2. The analog approach of the circuit

b) The digital approach (on/off), where the small activation device detects a closed circuit (or not) at each pill position in the blister (Figure 3). In this approach, the circuit would be produced with a single type conductive ink.

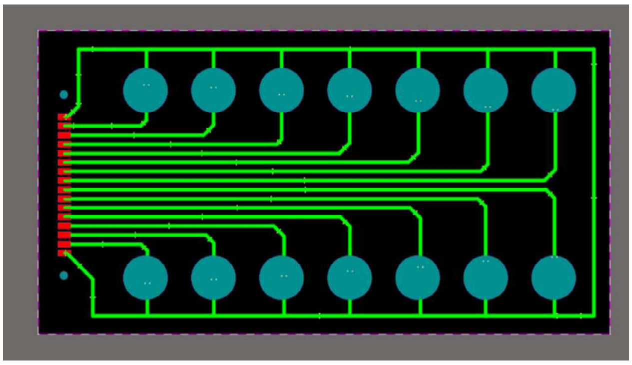

Figure 3. The digital approach of the circuit.

After several experiments and careful consideration of the advantages and disadvantages of the two aforementioned approaches, the authors decided that the one that best fits the goals of the Smart-Blister project is to continue with the digital approach (on/off).

For the production of the digital passive circuit two different methodologies were studied, namely, the electronic circuit directly screen printed onto the blister or onto a self-adhesive substrate (smart-label approach and subsequently transferred to the blister foil) using a conductive ink.

A. Printing the circuit directly onto the foil of the blister

In this approach, conductive ink of single walled carbon nanotubes (SWCNTs) in solvent isopropanol (Isopropanol: IPA) was used (70-80€/ ltr), which allows the printed circuit to be dried at temperatures ca. 40º-50º C. The consumption of ink for a single circuitry in each blister was approx. 1 ml. This results into 0.07-0.08€ as the material cost of each printed circuitry. Additionally, the screen printing should be taken into account as the "process" fabrication cost, which is extremely low, i.e. in a single day more than 10,000 circuitries could be printed with a screen printing machine; therefore this is considered to be negligible. The above calculations directly prove the main advantage of this work, which is the low-cost fabrication of printed smart circuitries, allowing the fabrication at large-scale, thus decreasing even further the overall cost and allowing the realization of the practical application of the proposed technology into the pharmaceutical and biomedical products market. Using ink that dries at low temperature was deemed necessary because the circuit would be screen printed on the back of the foil of the blister, which contains sensitive material, as pills are. In addition to that, the plastic material of the blister consists of a thermoplastic material which starts to soften at temperatures of 70º-80º C, probably reaching the glass transition temperature (Tg) of the polymer / plastic material. For these reasons, in this approach, an ink capable of drying in low temperatures (T<50º C) was chosen for screen printing of the circuitry. Moreover, it should be mentioned that the aluminum (Al) foil of the blister allows the printing of the conductive circuitry since inherently it has a dielectric layer typically used to avoid oxidation of the Al foil, as well as improving and increasing the barrier properties. This thin layer allows the printing of the circuitry without a short circuit across and between the printed lines.

For the printing process, a semi-automatic flatbed screen printing Machine (ATMA-60PD Digital Electric Flat Screen printer) has been used, utilising a 120-mesh polyester screen printing mesh, which allows the printing of quite fine printed features (even microelectronic circuits). For the screen printing, a relatively hard spatula / squeegee has been used, namely, parallelepiped rectangular shape, made of polyurethane with a hardness of 70 on the shore A scale, while the angle between the squeegee and the substrate plane was 45°. The printing speed was found to be the most suitable at 200 mm/sec, while the pressure of the squeegee on the mesh and the distance from the blister foil, used as the substrate, were optimized in the original prints before the final printing.

All the stages of directly printing SWCNT ink onto the blister foil are illustrated in the Figure 4 below. Note that the final product was protected by an adhesive vinyl foil properly designed and perforated in the pill positions to protect the printed circuit.

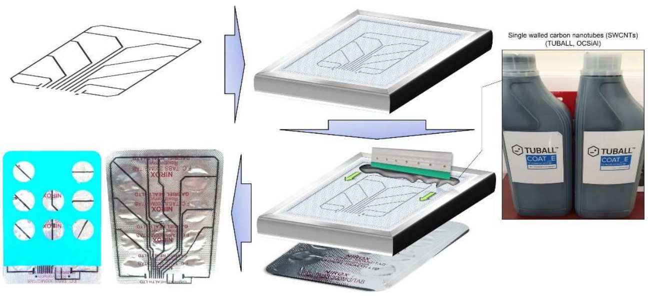

Figure 4. The approach of printing the circuit directly on the foil of the blister using a SWCNT ink.

B. *Printing the circuit on a self-adhesive paper foil that will be used as smart label*

In this approach, the printing procedure was the same with the one described above, with one main difference, the substrate used to print the circuitry. In this approach, a paper foil/ substrate with adhesive was used, which was then applied/ transferred on the backside of the foil of the blister as a "smart-label". Another significant difference is that the ink used for the screen printing was a nano-silver paste from Agfa (2,800-3,000 €/ kg), since it can yield lower resistance printed circuitry/ lines compared to the SWCNT ones, as well as it exhibited better wettability and printability with the underlying and targeted substrate (paper). It should be mentioned that the Ag-paste does not allow direct printing onto the blister since the plastic material could not resist the temperature needed for the Ag-paste/ ink to be dried and annealed (>130ºC). After printing, drying at 140º C took place for 10 minutes to completely dry the silver paste but also to obtain metallic conductivity (typically <1 Ohm by measuring with two electrodes at a distance of 1 cm interelectrode distance or in conductivity values; $\sigma > 10^6$ S/m). The consumption of paste for a single circuitry in each self-adhesive foil (the smart-label approach) was approx. 0.015g, which results into 0.042-0.045€ as the Ag-paste material cost of each printed circuitry. Additionally, the screen printing should be taken into account as the "process" fabrication cost, which, as previously for the SWCNT printed circuitry, could be considered to be negligible. The calculations directly prove also that the Ag-paste smart label approach is very promising and low-cost, allowing the mass production of smart blisters and potentially integration into the future pharmaceutical blisters. All the stages of the methodology B for the preparation of the mesh, the screen printing parameters, the paste used, etc., as well as the final product are presented in the Figure 5 below. Note that, once again, the final product was protected by adhesive vinyl foil properly designed and perforated in the pill positions to protect the printed circuit.

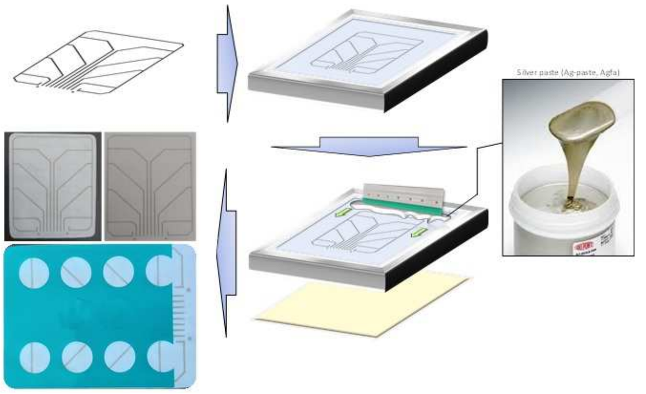

Figure 5. The approach of printing the circuit on a self-adhesive paper foil that was used as a smart label.

After several experiments and careful consideration of the advantages and disadvantages of the two aforementioned approaches, the authors decided that the one that best fits the goals of the Smart-Blister project is to continue with the "smart-label" approach. The main reasons for that choice were:

a. Conductive carbon nanotube ink printed directly on the metal / metal oxide substrate of the blister foil did not behave well electrically when the circuit broke due to the extraction of a pill from a random position. This is because it is very likely that the metal oxide has some discontinuity so that the conductive ink comes in contact with the metal foil of the blister and therefore, undesirable electrical behavior and short-circuit phenomena might occur.
b. The silver paste used showed perfect printability on the paper substrate which is low-cost and recyclable.

IV. Blister Activation and Communication Electronic Device (Actuator)

Blister activation and communication electronic device (actuator) composes the link between the identification circuit of the blister, the Central Information System, but also the patient. It has the crucial role of receiving the information of taking a pill, as well as its transmission to the Central Information System (Figure 6).

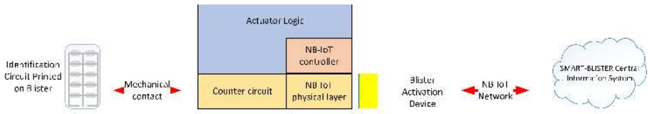

Figure 6: NB-IoT Actuator functional architecture

The actuator device has a minimum functionality: (i) powers the blister identification circuit, (ii) takes measurements about pill removal and (iii) exchanges information with the Central Information System through NB-IoT networks. Patient receives notifications about taking a pill and interferes with smart-blister system through the smart-blister mobile application or web interface.

Each actuator latches to one blister and has physical contact with the blister identification printed circuit through pogo pins (Figure 7). The actuator periodically powers the printed circuit and counts the remaining pills in the blister. If the physical contact breaks, the actuator generates an alarm. Every message (pill removal and alarms) propagates to the Central Information System through NB-IoT network and IoT platform.

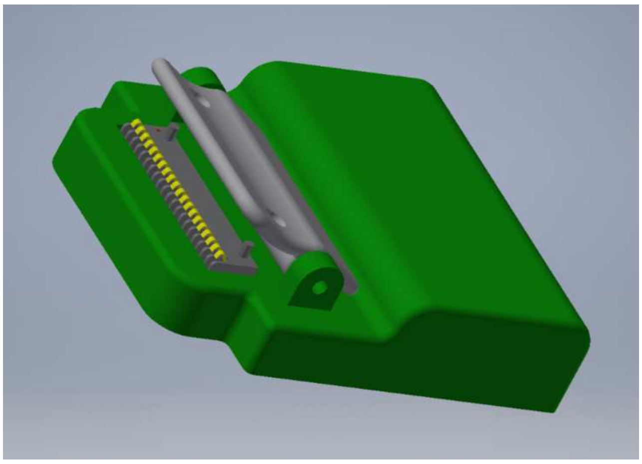

Figure 7. The blister activation and communication electronic device (actuator)

The actuator has minimum power consumption in order to be able to operate for several months without battery replacement or recharge. The detection of the condition of the circuit on the blister can be done by a low consumption microcontroller in 1ms and does not need more frequent sampling than 1sec. Using for example the ST STM32CubeMX consumption budget tool for the STM32L100 low-power microcontroller, and setting 1sec as the parameter, it turns out that the average consumption is about 30μA @ 3V (90μWh).

At the same time, the power consumption of the Nordic nRF9160 rev2 IoT microcontroller by uploading 1 measurement per minute has a power consumption of about 1.33mA @ 3.7V (4.921mWh) [19].

So, the actuator device can be powered by a battery of 875mAh approximately for a month.

Two microcontrollers are used: the ST STM32CubeMX for the detection of the condition of the circuit on the blister and the Nordic nRF9160 rev2 IoT microcontroller for the implementation of business logic and communication with IoT platform.

As far as the cost of the actuator is concerned, for quantities of 1000 pcs, it is estimated to be below 80 €.

System interaction with the patient is performed through the smart-blister mobile application or web interface. This approach of a parallel communication channel with the patient gives all the advantages of Android or iOS operating system (notifications, full graphical UI).

As part of Smart Blister project, two more approaches of actuators have been studied:

a. Blister activation device with minimum functionality (i) powers the blister identification circuit and takes measurements and (ii) interconnects with the Central Information System through a mobile terminal via its low power Bluetooth (BLE) interface. The mobile terminal runs the smart-blister mobile app. This type of actuator has extremely low power consumption, but it is dependent on a mobile terminal to function. Thus, this approach was rejected as more complicated and error prone for the user. The user (patient) still receives notifications and interacts with the smart-blister system via the smart-blister mobile application and web interface.

b. Blister actuator device with full functionality without the requirement of a mobile terminal, mobile app or web interface for the user. The actuator is connected directly to the Central Information System via WiFi or 4G. It transfers the count of pills to the Central Information System and receives notifications to the user from it. The actuator itself informs and interacts with the user through an embedded touch screen. This approach is a stand alone approach but with significant incremented cost.

V. Central Information System for Data Collection and Dosage Scheduling

The innovative services of Smart-Blister are implemented in the Central Information System. All electronic blister activation devices must be interconnected with the Central Information System, using existing telecommunication infrastructures (Figure 8). The Central Information System is responsible for initializing actuators, gathering all pill data, storing all the information, calculating medication schedule, managing the users, interacting with them through web UI and executing all use cases.

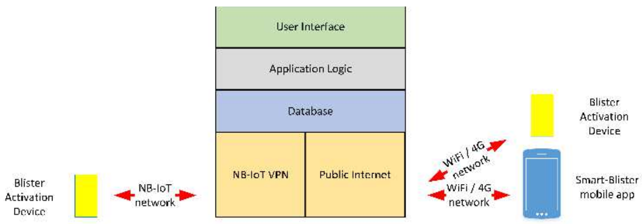

Figure 8: Central Information System General Architecture

Initially, through the web interface of the Central Information System, the pharmacist activates an actuator device and matches it with specific patient and medication. During the initialization process, the pharmacist input in the system the dosage, dose frequency, and duration of treatment of the drug prescribed to the patient. The Central Information System calculates a dosage schedule for each actuator.

After actuator initialization, the patient receives notifications about taking a dose. After the pills are removed by the patient, the actuator counts them and sends the measurement to the IoT platform of the Central Information System. The system records the transaction and determines if the patient received the correct dose. If not, it notifies the patient and the caregiver to act.

As part of Smart Blister project, Amazon Web Services (AWS) IoT platform was chosen in order to interconnect the actuator with the Central Information System. Specifically, MQTT topics were used to identify AWS IoT messages. AWS IoT clients identify the messages they publish by giving the messages topic names. The Central Information System identify the messages to which they want to subscribe (receive) by registering a topic filter with AWS IoT Core. The treating physician, after the relevant approval from the patient, is able through the Central Information System, to monitor the patient's compliance with the medication and in cooperation with him to modify or redesign it for better results.

Finally, the Central Information System will produce statistical reports related to patient's medication adherence. During the fusion of data, all personal information, as name, surname, social security number, etc. will be pseudonymized before data merging. After data merging, there will be an anonymization process so as the final reports will not contain any personalized data according to the General Data Protection Regulation (GDPR).

VI. Conclusions

In the present work, a medication adherence system was described and developed. The system comprises a newly designed smart label and specifically a passive electronic circuit printed on a self-adhesive paper that can be applied to a medical blister and a small electronic device which activates the blister and communicates with a central information cloud computing system. The Central Information System consists of a web application which collects all the medical adherence-related data and notifies the system's end-users accordingly.

The main novelty of the presented work is the use of conductive inks for printing one-layer electronic circuits on mass produced blisters. The advantage of the method is that it can be easily adopted with low cost in the mass production of smart blisters. Moreover, the proposed activation device is reusable, it can be used with various blisters and it is expected to be of low-cost.

Future work will focus on enhancing data processing capability and system scalability towards incorporating more devices. Additionally, a properly designed study will be carried out to assess the potential of the proposed smart labels on medical blisters along with prototype devices for increasing medication adherence.

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