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Diagnostic and therapeutic devices based on polymeric microneedles:

fabrication and preliminary results.

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***Abstract*— Applications of microneedles in biomedicine wide range from diagnostics to therapeutics. This crucial and versatile tool is the interface between the human body and often a complicated device. We present two sensing device based on hybrid microneedles array for diagnostic and therapeutic applications. The hybrid microneedles was fabricated by using a commercial photocatalyzer to solidify a liquid PolyEthylene Glycol hydrogel. After polymerization, the MNs have a porous structure, which can include a variety of biological molecules, as bioprobes or drugs. The first device presented is an electro-chemical sensor where microneedles include enzymes in their matrix that interact with glucose. It is fabricated by plating with gold the MNs and etching their tips. The redox reaction with glucose, mediated by ferrocene, creates a charge transfer resulting in a current proportional to the glucose concentration. The second device is a therapeutic tool with an optically controlled release of drugs. In this case the device includes a porous silicon membrane with a Bragg's mirror, whose reflection wavelength is related to the drugs concentration in the MN.**

Keywords—component; formatting; style; styling; insert (key words)

I. INTRODUCTION

Exploiting technologies and facilities for Micro and Nano Electro Mechanical Systems (MEMS and NEMS) fabrication, a new kind of biomedical devices has been realized and developed. This devices are able to control their chemical and physical characteristics on a very small scale, till few nanometers, gaining popularity in biomedicine field over the last decade [1-3]. Among these, microneedles (MNs) are essential components for such biomedical systems, acting as interface between the device and the body of the patient. The density matrix, the material, the length, the shape of the body and the tip of the MNs drastically vary depending on the application [2,3]. In fact, MNs applications range from the drug and gene delivery to the fluid extraction, from the cell therapy to the diagnostic tools [1-4]. We present two sensing device based on hybrid microneedles array for diagnostic and therapeutic applications. The versatility of the basic material (PEG) was the key to cover a wide range of application. Also, its hydrogel nature allows the casting and the directly polymerization, by eliminate the etching step in the fabrication process and by drastically decrease the cost of realization.

II. FABRICATION AND CHARACTERIZATION

A. Fabrication

All chemicals are commercially available and used as received. A solution of PolyEthylene (Glycol) DiAcrylate (PEGDA, number average molecular weight, Mn=250, purchased by Sigma Aldrich) and 2-Hydroxy-2-methyl-1-phenyl-propan-1-one (DAROCUR© 1173, Basf) at 2% volume/volume concentration has been used to fabricate the MNs array and his substrate support. The liquid DAROCUR© initiates the polymerization of the PEGDA hydrogel, by exposing the solution at UV light. A sketch of fabrication process is shown in fig. 1. Several times of exposure has been used to define the shape and the length of MNs.

A substrate layer has been fabricated on a UV transparent support by exposing the polymeric solution at UV light without any photomask (see the first step in fig. 1). The quantity of 1mL of polymeric solution has been casted into a vessel 4mm high (see the second step in fig. 1). Such solution is exposed to UV light after the flipping of the substrate layer and the transparent support on the vessel (see the third step in fig. 1). In a such case a photomask with an holes array is used. The UV light goes through the holes in the mask, the UV transparent layer and the support layer and exposes a portion of polymeric solution. The cone shape of the MNs is obtained from the exposure light cone with higher intensity. Finally, the MNs are developed in deionized (d. i.) water.

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The polymeric matrix of the solidified MNs can incorporate molecules that can be locked or released depending on the molecules size. When the PEGDA is soaked in a aqueous solution the matrix swells and the release of molecules is related to the relative length of the polymeric cross-link and the size of the molecules.

Vice versa, small molecules can enter into the swelled MNs and interact with trapped molecules.

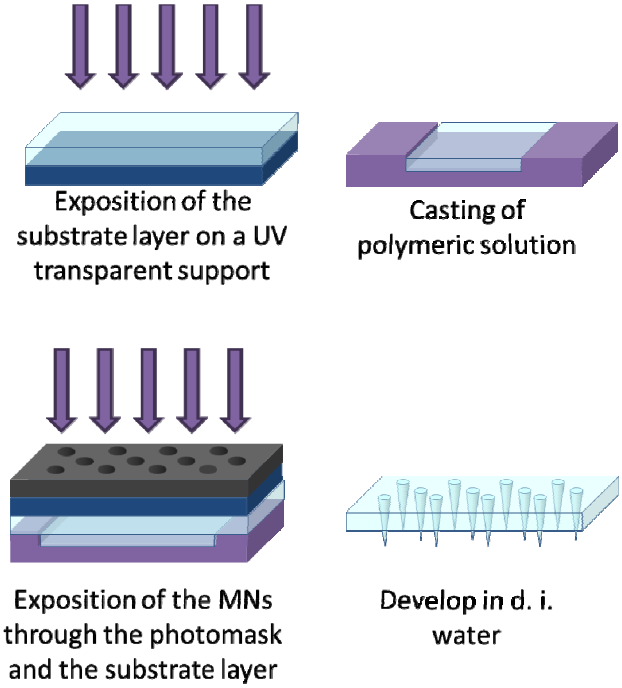

Fig. 1. Sketch of fabrication process. In the upper left side, the first step of the fabrication: the exposition of the substrate layer on a UV transparent support. In the upper right side, the second step: the casting of the polymeric solution into a vessel. In the lower left side, the third step: exposition of the MNs through the photomask, the transparet support and the substrate layer. In the lower right side, the final step: the develop in the d. i. water.

The optical structure is fabricated by means of electro-chemical etching of a crystalline silicon wafer. In presence of a HF based solution, two current intensities have been used to fabricate two kind of porous layers, that have two kind of refractive index. The layer with lower porosity, generally, has a higher refractive index, with respect to the higher porosity layer, according to the Bruggeman approximation [5]. Repeating a such couple of layers, it is possible to obtain a Bragg's Mirror (BM) that reflects a band of wavelengths. The center of the reflected band is related to the drugs concentration. A sketch of fabrication process is shown in fig. 2(a). The fig. 2 (b) shows a picture of the device1.

The BM in the device1 has been loaded with fluorescein molecules. The loading results in a change of color of the BM.

After assembling of the device2 the fluorescein diffuses into the polymeric matrix, by emptying the BM. In this way the BM changes again color.

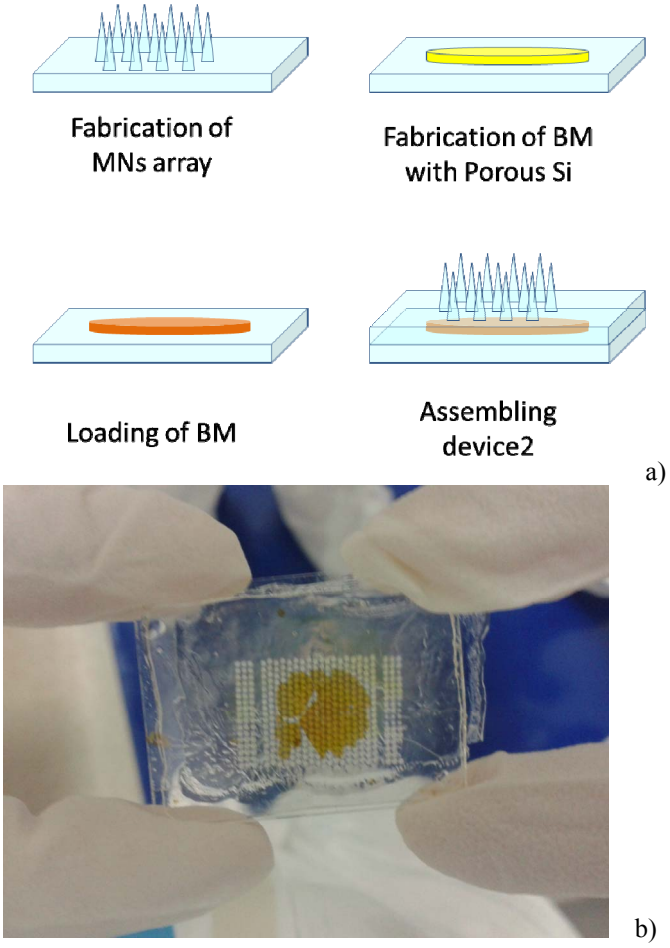

Fig. 2. a) Sketch of fabrication process of the device1. b) Photo picture of the device1 after assembling.

The electrochemical sensor (device2) is fabricated by adding an enzymatic solution in the polymeric solution before to expose it at UV light and by plating with gold the polymerizated MNs. In this case the enzyme molecules are fabricated together with the MNs and don't diffuses into the polymeric matrix. The fig. 3 shows a sketch of the fabrication process of the device2. In the upper side of fig.3, the first step of the fabrication of device2 is shown. The fabrication of MNs follows the general fabrication steps above described (see fig.1), but is added an enzymatic solution in the vessel. The second step is the gold plating of the MNs. In the final step, the tips of the MNs have been etched (fig. 3).

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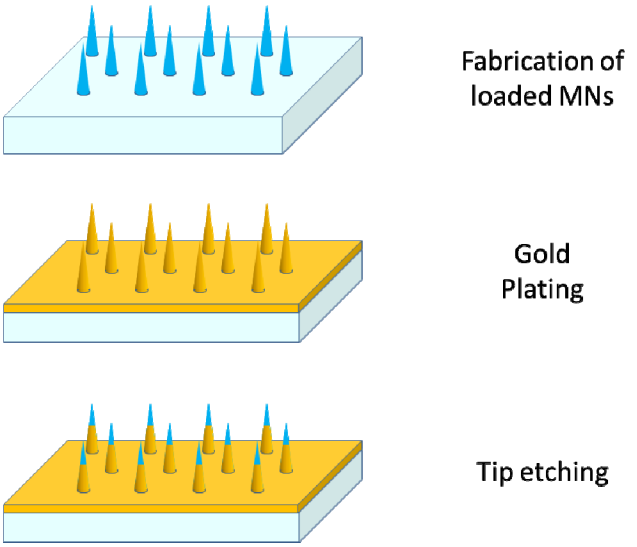

Fig. 3. Sketch of fabrication process of the device2. In the upper side, the fabrication of MNs follows the general fabrication steps above described (see fig.1), but is added an enzymatic solution in the vessel. The second step is the gold plating of the MNs. In the final step, the tips of the MNs have been etched.

In the device2 the uncovered tips allows to the glucose molecules to diffuse into the polymeric matrix. The gold electrode, at potential 300mV, captures the electrons produced during the oxido-reductase reaction.

B. Characterization

A sketch of working of the two devices is shown in fig. 4.

As described before, the polymeric matrix of the solidified MNs can incorporate molecules that can be locked or released depending on the molecules size. When the PEGDA is soaked in a aqueous solution the matrix swells and the release of molecules is related to the relative length of the polymeric cross-link and the size of the molecules. Vice versa, small molecules can enter into the swelled MNs and interact with trapped molecules. In the case of the device1, fluorescein molecules have been used as proof of concept. Fluorescein diffuses from the BM to the polymeric matrix and can be released into the interstitial liquid.

In the device2, the GOX enzymes (red half annulus in fig.4) are locked into the MN of device2, whereas the glucose present in the interstitial liquid can diffuse into the polymeric matrix.

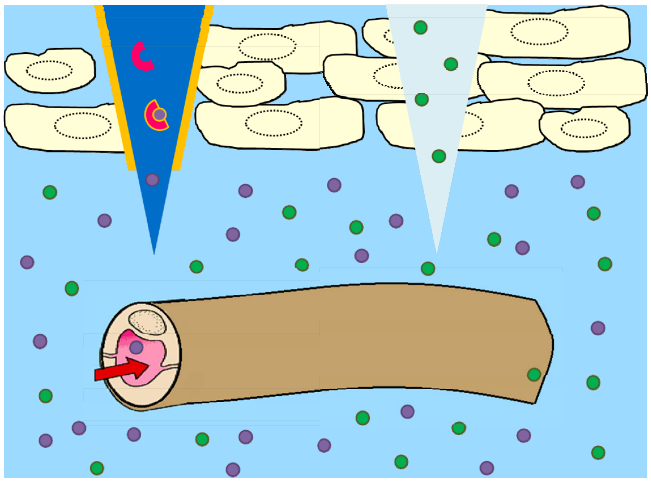

Fig. 4. Sketch of working of the two devices. In the right side, a MNs of the device1 overcomes the corneum stratum and releases drug molecules (green circles) into the interstitial liquid. In the left side, the GOX enzymes (red half annulus) locked into the MN of device2 interact with the glucose present in the interstitial liquid.

The first proof of working of the device1 has been provided by the fluorescence microscopy. In fig. 5 and 6, images have been performed after 2 hours from the loading of the BM.

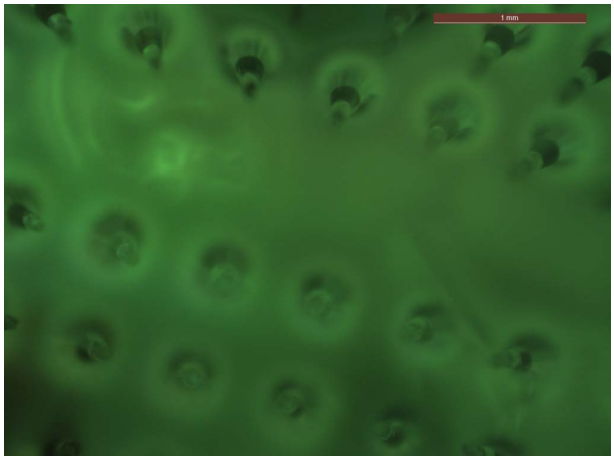

Fig. 5. Top view of the device1 in fluorescence mode.

From the top view of the device1 in fluorescence mode (fig. 5), it is clear that the fluoresceine is transferred from the BM to the MNs and it is quite omogeneusly distributed into the PEGDA matrix of MNs.

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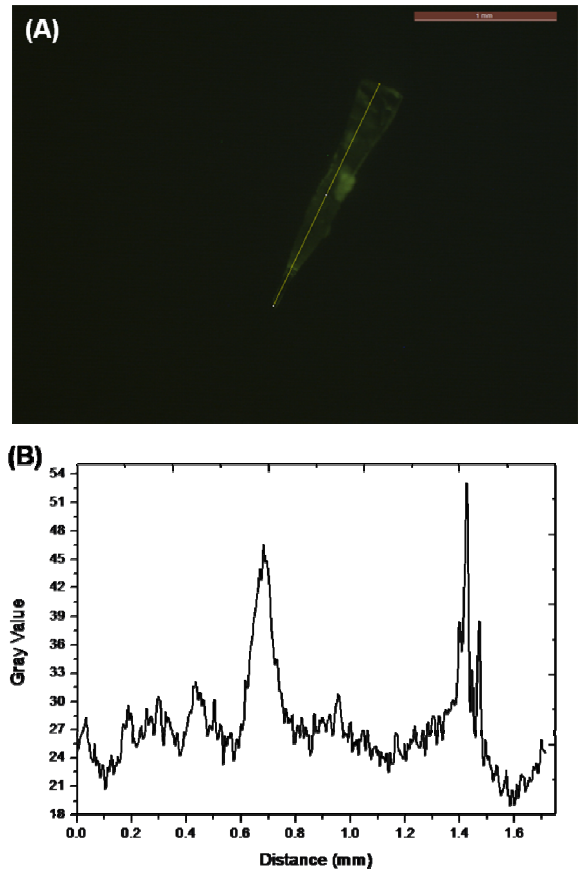

Fig. 6. The image (A) shows a microneedle isolated from the rest of the device, upon interaction with fluorescein. The graph (B) shows that the grayscale profile of the microneedle (along the yellow line of the image (A)) is quite uniform (27 ± 5), then the fluorescein is evenly distributed throughout the microneedle.

Also, a single MN detached from the device has been analyzed in order to demonstrate that not only the substrate layer is infiltrated with the fluorescein. The image (A) in fig. 6 shows a microneedle isolated from the rest of the device, upon interaction with fluorescein. The graph (B) in fig. 6 shows that the grayscale profile of the microneedle (along the yellow line of the image (A)) is quite uniform (27 ± 5), then the fluorescein is evenly distributed throughout the microneedle.

In the device2, the locked enzymes is the glucose oxidase enzyme (GOx) (EC 1.1.3.4), an oxido-reductase that catalyses the oxidation of glucose to hydrogen peroxide and D-glucono-δ-lactone. During the oxido-reductase reaction, the production of electron can be monitored as current by applying a small potential (300mV).

A preliminary result of the electro-chemical measurements are shown in fig. 7, where a linear dependence of the current from the glucose concentration in a PBS solution is evident.

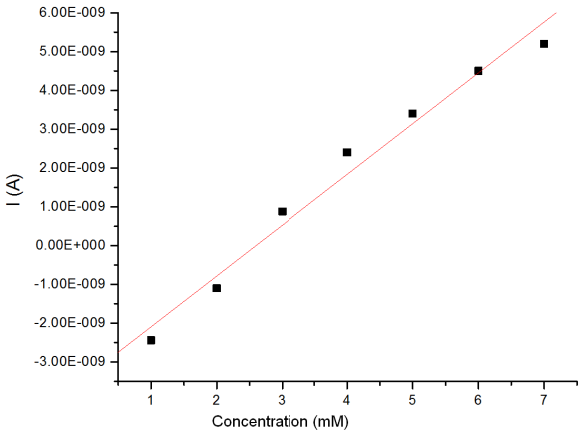

Fig. 7. A preliminary results of electrochemical measurements. The current increase by increasing the concentration of glucose into the PBS solution.

III. Conclusions

Polymeric MNs have been fabricated by means of direct photolithography. The MNs the solidified MNs can incorporate molecules that can be locked or released depending on the molecules size. Based on this feature, we presented two devices for delivery and sensing of small molecules.

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