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Conductive Composite Microneedle Sensors based on Cellulose Acetate Phthalate: Investigating Performance and Biodegradability

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Abstract— Conductive microneedle patches based on carbon nanoparticle composites in which cellulose acetate phthalate (CAP) or polystyrene (PS) acted as a binder were investigated. The electrochemical properties of the composite system were assessed using ferrocyanide as a redox probe and compared to screen printed carbon electrodes. Preliminary investigations of biodegradability were conducted with the influence of soil interment assessed by electron microscopy. While the PS microneedles exhibited no breakdown, the CAP systems were found to be substantially degraded after 1 week with complete removal of the needle tips and hence piercing capability.

Index Terms—Sensor, Composite, Biodegradable, Electrode, Microneedle

I. INTRODUCTION

The home glucose market in particular has, at least until recently, been dominated by screen printed electrodes but these still require the use of finger prick testing which can be painful and will inevitably generate considerable waste (strip, lancet, insulin syringe/ needle etc) [1,2]. There is a pressing need to reconsider the design, application and disposal of modern point of care (POC) sensing consumables to provide more sustainable options that avoid the accumulation of waste. It is within this remit that microneedles sensors have emerged as potential solutions offering pain free sampling and analysis and possible avenues to minimising waste. Dissolving / biodegradable microneedles for vaccine delivery have been heralded as a means of avoiding the waste associated with conventional syringe delivery methods [3-5] but the formulations used to provide the structural component of the needle may not be best suited to designs employed for sensing purposes. In this communication we have sought to explore the design and characterisation of composite microneedle patches which possess electrochemical characteristics consistent with screen printed electrodes whilst providing a facile route through which the spent device could be disposed.

The design and production of microneedles intended for electrochemical sensing applications has seen a wide variety of strategies adopted and these have been extensively reviewed [6,7]. In most cases, moulds based on PDMS tend to be the replication workhorses and offer an easy route through which to manipulate the material composition of the MN and thereby refine its properties [7-11]. This micromoulding approach has obvious advantages for drug delivery applications - providing a simple means through which to incorporate the therapeutic agent, but it has also been shown to enable the production of MN arrays for sensing applications. The potential

viability of the approach was initially demonstrated using composite palladium / polycarbonate and nanocarbon/ polystyrene MN structures [12,13]. Moreover, the rich interfacial chemistry of the carbon surface can enable the immobilization of enzymes (ie.via carbodiimide coupling with the surface carboxyl functionalities) [13].

While there is an extensive literature base on the use of dissolving or swellable microneedle formulations [3-5], it must be noted that in this particular case, premature dissolution of the needle component would destroy the electroanalytical capability. The ideal polymeric binder must be stable under a given set of conditions for a duration appropriate to collect the target data, but which would, over a more moderate period, dissolve leaving only the carbon residue. Cellulose acetate phthalate (Fig 1) was selected as the binder here on the basis that it is chemically and mechanically stable in acid condition but dissolves in mildly alkaline media and is widely used as an enteric coating for oral tablets to enable transit to the intestine [14,15].

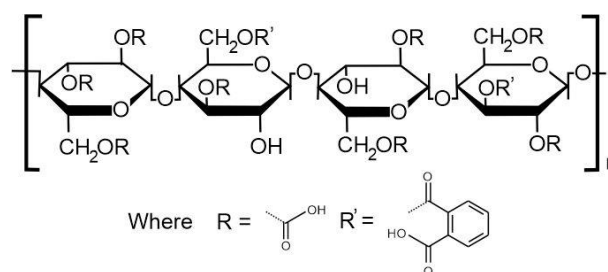


Fig. 1. Cellulose acetate phthalate

The development of a cellulose acetate phthalate – carbon microneedle was therefore proposed as a means of facilitating the single step fabrication of a disposable sensor system offering both enhanced electrochemical performance and biodegradability

II. EXPERIMENT DETAILS

Carbon nano powder (<100 nm), polystyrene (MW 192,000), cellulose acetate phthalate (MW 2534) were obtained from Sigma-Aldrich, were the highest grade used without further purification. Britton Robinson buffers (acetic, boric, and phosphoric acids, each at a concentration of 0.04 M and adjusted to the appropriate pH through the addition of sodium hydroxide) were used throughout unless otherwise specified. Microneedle moulds were obtained from Micropoint Technologies Pte Ltd (Singapore) and were pyramidal in format with 200 (base) x 500 (pitch) x 700 (height) micron dimensions covering a 10 x 10 needle array. Electrochemical analysis was carried out using a Palm Sens computer controlled potentiostat with a standard three-electrode configuration in which the microneedle patch was used as the working electrode with platinum and a Ag/AgCl half cell (3M NaCl, BAS Technicol UK) acting as counter and reference respectively. All measurements were conducted at $22^{\circ}\text{C} \pm 2^{\circ}\text{C}$. Conductivity measurements were obtained using a 2461 series SourceMeter® (Keithley) 4 point probe. The conductivity of an unmodified carbon-polystyrene microneedle patch was found to be $1575.2 \text{ S/m} \pm 96 \text{ S/m}$ ($N = 5$).

Carbon nanoparticles were combined with the polymer (polystyrene powder or cellulose acetate phthalate) in a ratio of 1:1 by weight, dissolved in cyclohexanone and stirred until a homogenous solution was obtained (typically 2 hours). The solution was cast into silicone microneedle templates and a carbon fibre stub placed into the base plate to facilitate electrical connection. The moulds were placed in a vacuum at 30°C and the pressure increased to 1000 mbar and the air released again (to force the homogenous solution to the tips of the mould ensuring sharp microneedle production). The templates were topped up with more solution - preferably overflowing the cast to allow for solvent evaporation. The solvent was left to evaporate at room temperature (over 48 hrs) whereupon the needles could be removed from the mould (Fig 2).

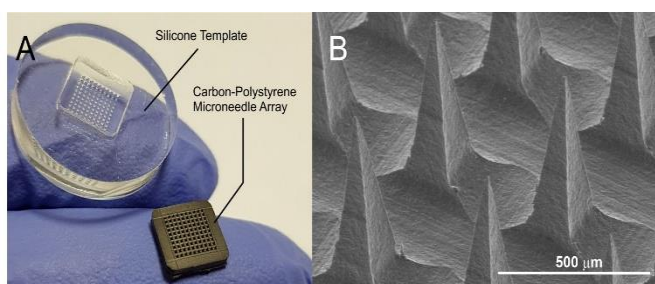


Fig 2. (A) Silicone mould and resulting composite microneedle patch. (B) Electron micrograph of carbon composite microneedles (200x200x700 micron with 500 micron spacing)

The baseplate and non-needle surfaces of the resulting microneedle array were coated with enamel (6 hour drying period) to serve as a dielectric and define the geometric electrode area (0.603 cm^2).

III. RESULTS AND DISCUSSION

Screen printed carbon electrodes (SPCE) form the backbone of home glucose monitoring and provide an inexpensive substrate that is inherently scalable. Cyclic voltammograms detailing the response of a SPCE (working area: 0.00785 cm^2) towards ferrocyanide (2 mM, 0.1 M KCl) is shown in Fig 3A with a large peak separation characteristic of slow electron transfer at the graphitic carbon. Electrochemical pre-treatment of the surface through oxidation in NaOH results in the partial exfoliation of the carbon and the incorporation of oxygen functional groups into the carbon lattice [16]. This results in a much improved electrochemical profile with a peak separation approaching the theoretical Nernstian value of 60 mV.

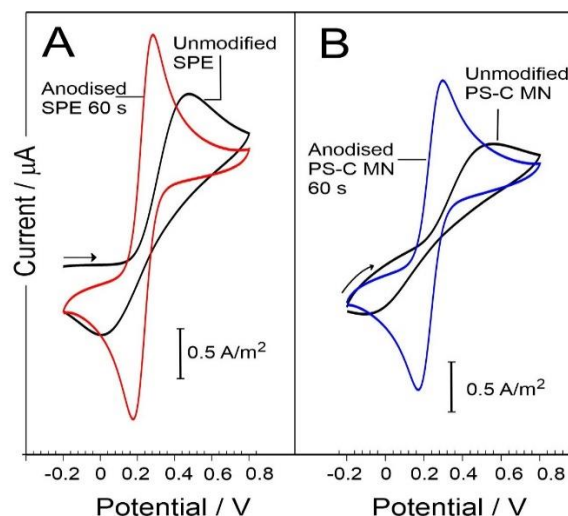


Fig 3. Cyclic voltammograms detailing the response of a (A) screen printed carbon electrode and (B) Polystyrene-carbon microneedle to ferrocyanide (2 mM, 0.1 M KCl, 50 mV/s) before and after electrochemical anodisation in NaOH (0.1 M, +2 V, 60 s)

The carbon microneedles, like the SPCE, are composed of graphitic carbon encapsulated in a polymer matrix (typically polystyrene or polycarbonate) but rather than being predominantly 2D – the polymer must provide the structural integrity to support the 3D needle projections. The electrochemical performance (Fig 3B) is analogous to that of the screen printed system where the unmodified system can be dramatically improved after electrochemical anodisation.

While post fabrication modification of the MN can certainly improve the electrochemical performance of the system, it creates considerable difficulties from a manufacturing perspective. The additional step is time consuming to configure and deploy. It must also be noted that the use of polystyrene in this instance also creates issues in terms of the biodegradability of the microneedle array itself. Switching to cellulose acetate phthalate as the core binder was anticipated to address the challenge of biodegradability. Electron micrographs highlighting the dissolution of the CAP polymer in pH 8 Britton Robinson buffer after 1 min and 30 minutes are highlighted in

Figs 4A and 4B respectively and stand in marked contrast to the needle structures shown in Fig 2B and recorded prior to any treatment. Moreover, microneedle arrays formed from PS-C formulations did not exhibit any pH sensitivity and remained unchanged.

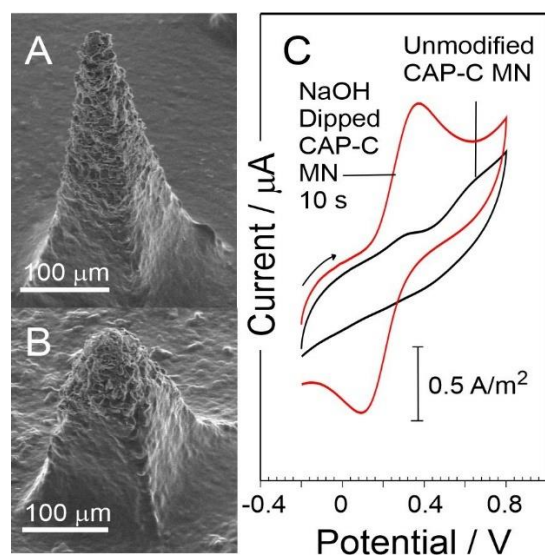


Fig. 4. SEMs of the CAP-C MN after exposure to pH 8 Britton Robinson buffers for (A) 1 min and (B) 30 min. (C) Cyclic voltammograms comparing the response CAP-C MN to ferrocyanide (2 mM, 0.1 M KCl, 50 mV/s) before and after treatment with NaOH (0.1 M, 10 s)

There is a gradual dissolution of the CAP material in the alkaline solution with prolonged immersion (>30 min) leading to substantial loss of needle definition. Cyclic voltammograms detailing the response of the CAP-C MN system, under conditions similar to those used previously for the polystyrene system (Fig 3B) are detailed in Fig 4C. The redox peaks associated with the oxidation and reduction of the ferrocyanide are barely visible with the oxidation process observed as a poor defined broad peak at +0.6 V. The large overpotential needed to induce the oxidation of the ferrocyanide at the unmodified CAP-C is consistent with the response observed with the unmodified polystyrene system. In contrast to the latter however, the CAP-C MN array exhibits a large capacitive background which could be attributed to the hydrophilic nature of the binder and the potential swelling of the latter at the microneedle interface.

While the response of the PS-C MN systems could be improved through the additional anodisation step, the same cannot be employed in the case of CAP-C systems where prolonged immersion in NaOH would lead to the sustained dissolution of the needles (as indicated in Fig 4A and 4B) and loss of mechanical integrity. The dissolution of CAP in alkaline conditions was hailed as a core feature of the proposed design – allowing facile biodegradation. However, it was postulated that short exposure (10s) to alkali may serve as a viable pre-treatment option which would remove interfacial CAP without unduly compromising the needle itself. The voltammetric response of the CAP-C MN after exposure to NaOH for 10s is included in Fig 4C for comparison. The cyclic voltammetric profile is significantly improved in terms of the peak magnitude and definition where the characteristic “duck” profile is apparent. This improvement in

performance is attributed to a cleaning effect whereby the CAP film at the carbon particle interfaces is removed thereby exposing underlying carbon. It should be noted that similarly dipping an unmodified PS-C MN into NaOH without the application of an oxidation potential did not lead to any improvement in the cyclic voltammetric response. This could be attributed to the insoluble nature of the polystyrene in aqueous solution. A more detailed examination of the dissolution of the CAP-C MN in pH 7 BR buffer is shown in Figure 5. The electrode is only stable for up to 10 minutes before the steady degradation in response is observed. While this precludes long term monitoring applications, it could be useful for single use, point of care scenarios where the measurement is performed shortly after insertion.

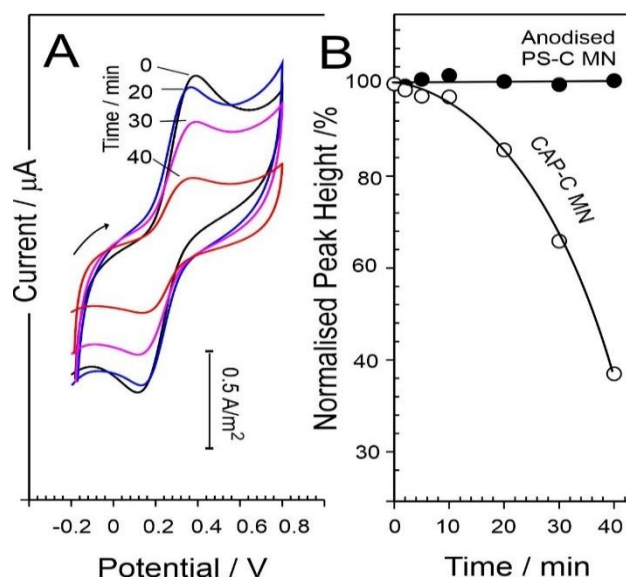


Fig. 5. (A) Cyclic voltammograms comparing the response of a CAP-C MN array to ferrocyanide (2 mM, pH 7 BR buffer, 50 mV/s) over time. (B) Comparison of changes of ferrocyanide oxidation peak height with time for both CAP-C and PS-C MN arrays.

The analytical capability of the CAP-C MN electrode array was assessed through the amperometric detection of peroxide (+1.0 V, 10s, pH 7 buffer). The current response was linear over the range 25 μM to 500 μM ($I / \text{A} = 0.0323 [\text{H}_2\text{O}_2 / \text{mol L}^{-1}] + 2 \times 10^{-8}$; $N = 6$; $R^2 = 0.998$) with a limit of detection of 5.7 μM (based on 3.3 S_b)

The stability of the CAP-microneedle systems was also assessed through examining the morphology after being interred in moist loam soil (in line with ASTM D5988 – 18 : Standard Test Method for Determining Aerobic Biodegradation of Plastic Materials in Soil) for 1 week. It was envisaged that a combination of environmental weathering and microbial processes should dissolve / metabolise the CAP binder resulting in the degradation of the MN array. Electron micrographs detailing the structural changes in the CAP-C microneedle before and after 1 week of being interred in the soil are compared in Figs 6 A-D. PS-C MN arrays were also included in the investigation to serve as a control and the electron micrographs recorded after 1 week of exposure are detailed in Fig 6 E-F.

The degradation of the CAP-C microneedle array is clear from the

electron micrographs and stands in marked contrast with the PS-C which are effectively unchanged (*cf.* Fig 2B). It is important to note that the CAP-C MN tips have been removed and hence their piercing capability. The latter is crucial from a health and safety perspective such that any inadvertent secondary application is avoided.

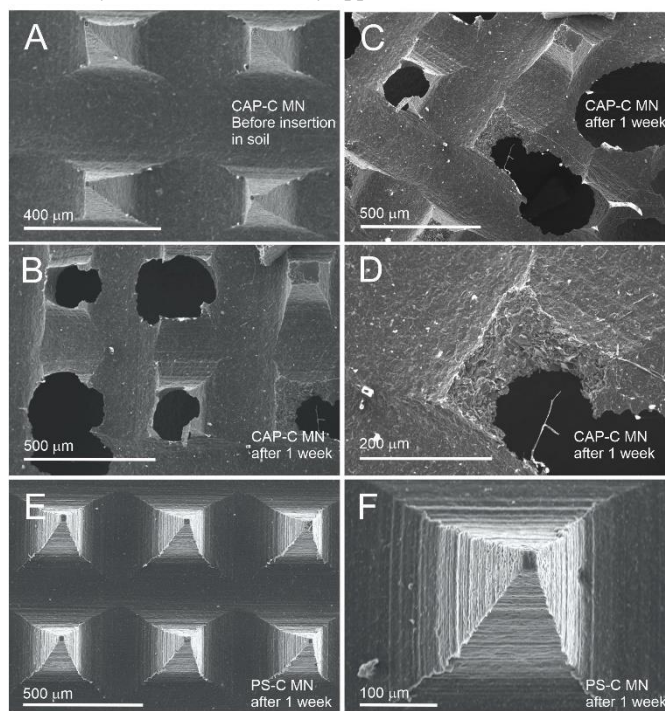


Fig. 6. Electron micrographs of the CAP-C microneedles before (A) and after (B-D) being interred in loam soil for 1 week. PS-C microneedles similarly interred for 1 week are detailed in E and F.

The rapid degradation of the CAP system advocated here stands in marked contrast to the degradation period expected for polystyrene or polycarbonate. It also improves the acceptability of disposing of the spent MN in domestic/household waste or composting recycling systems. This again is in marked contrast where current recommendations for the disposal of measurement strips and lancets employed in home glucose monitoring related to dedicated waste containers for incineration. There are long standing issues with compliance with prescribed disposal practices and it has been estimated by Thompson and Cook (2021) that in the UK almost 30% of lancets were placed directly into household waste [1]. Similar numbers have been reported internationally and contribute to a worrisome waste and safety problem [1,2].

IV. Conclusions

Waste from home diagnostics is a long standing issue exacerbated by poor compliance in relation to the appropriate disposal of spent test strip, lancets and syringes giving rise to health and safety hazards domestically and for those involved in the collection of the Cellulose acetate phthalate provides a biodegradable option – allowing more

sustainable disposal practices but without compromising the actual operational characteristics/performance of the device.

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