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Puttaswamy, S., Bandla, A., Fishlock, S., lee, S., Lee, C., & McLaughlin, J. (2018). *Hydrogel as a Nerve Guide and Biocompatible Glue for Neural Applications*. Paper presented at IEEE International Conference on Nanotechnology, Cork, Ireland.

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Publication Status:

Published (in print/issue): 28/01/2018

Document Version

Publisher's PDF, also known as Version of record

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Hydrogel as a Nerve Guide and Biocompatible Glue for Neural Applications

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Abstract— In the present work, Poly(ethylene glycol) (PEG) biocompatible hydrogel has been employed for two neural applications: nerve guide conduits and as an in-vitro neural bioglu. Nerve guide conduits (NGCs) are widely accepted in the treatment of peripheral nerve injuries. In the first application, we present the design of a simple and low-cost method to fabricate hydrogel-based NGCs. In this method we employ light curing method for 5 seconds to fabricate NGCs in a short span of time. The fabricated NGC was assessed in vitro to demonstrate the neural application. The efficient, low-cost and simple method proposed in this study addresses the limitations in existing expensive and time-consuming techniques of fabricating NGCs. Secondly, we demonstrate the application of PEGDA as an in-vitro neural bioglu. Micro electrode neural interface requires effective binding to achieve low signal-to-noise ratio during neural signal recording, hence there is a great demand for developing surgical glues which are nontoxic, biocompatible and which work well in highly corrosive environments within the body. We employed a photosensitive hydrogel, which can be cured within a few seconds to secure electrodes when interfaced with small nerves.

I. INTRODUCTION

Hydrogels, which are group of polymeric materials, are being explored to use in many tissue engineering applications. Poly(ethylene glycol) diacrylate (PEGDA) has been widely used in a number of applications due to its biocompatibility, non-toxicity and stability in corrosive environments. For example, PEDGA has been employed as a support to form 3-D environment for liver cells, insulating microstructure, cell encapsulation for transplantation, surgical barriers and drug delivery tools [1]–[5].

Peripheral nerve injury is a serious debilitating condition affecting trauma patients and often requiring surgical intervention. Autologous nerve grafts are currently the accepted gold standard, but are associated with a several major limitations such as surgical complications and donor site morbidity [6]. Alternatively, NGCs serve to guide the severed peripheral nerve regeneration, while also creating a favorable

micro-environment for nerve regeneration. Several materials and techniques have been explored for the purpose of NGCs. Synthetic polymers give versatility in design and controllability over stiffness and degradation rate, but these polymers may also induce undesirable immune responses and display varying resorption in the body [7]. Biological materials such as collagen and silk fibroin have advantageous properties such as cell binding domains, but also come with a potential risk of inflammatory response [8]. Hydrogels are used in numerous soft tissue biomedical devices; however, their use as NGCs has not been widely explored [9], [10].

Interfacing micro electrodes during nerve stimulation, or recording, requires precise positioning and firm contact. The strong electrode contact should be achieved without causing local tissue damage. Conventionally, researchers use suturing techniques which are time consuming, potentially damages the nerve, and are not suitable for complicated procedures. Employing biocompatible glues is a simple, effective, non-invasive method and provides an immediate waterproof seal. Glues which are currently available are expensive, have low adhesion strength [11] and are toxic [12]. These adhesives must be gradually metabolized and should not cause adverse effects on tissue interaction [13] and must also prevent tissue deformation [14]. Thus, there is a necessity to employ a material with all the above-mentioned characteristics. PEG is used both as a fluid barrier and as a hemostatic agent, and is biodegraded within 1–6 weeks.

In this study, we proposed the use of a photosensitive hydrogel, PEGDA, as a material for nerve guides and as biocompatible glue for neural interfaces. The results were tested in an *in vivo* application of a neural interface to the peripheral nerve. This demonstration of the use of PEGDA as an adhesive for neural interface applications has opened the possibility of extending scope to other *in vivo* applications requiring biocompatible adhesives.

II. RAT PREPARATION FOR *IN VIVO* TEST

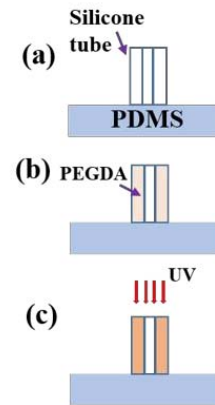
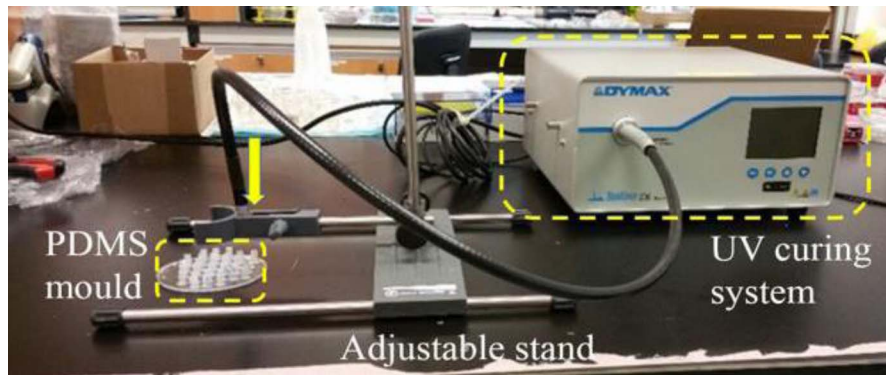


Fig. 1 Experimental set up for the fabrication of nerve conduit & fabrication procedure

All The experiments performed using an adult female Sprague Dawley rats (250 g) (In Vivos Pte Ltd, Singapore). Before starting any experiment, the rats were kept in the laboraroty for one week with food and water provided *ad libitum* and a cycle of 12 hours lights on/off. The animal care and use procedures followed as mentioned by the Agri-Food & Veterinary Authority of Singapore (AVA), the Institutional Animal Care and Use Committee (IACUC) and the ethics commission of the National University of Singapore. The rats were anesthetized with a single bolus injection of ketamine/xylazine (150 mg/kg and 10 mg/kg, respectively, intraperitoneal). The animal's head was then fixed in a stereotaxic apparatus and an incision made to expose the nerve after tolerable depth of anesthesia was reached. The rat hindlimbs were shaved from the knee to the hip using an electrical shaver. The sciatic nerve was exposed through a gluteal-splitting incision and dissected from the surrounding tissue. A similar procedure was followed to expose other types of nerve.

III. RESULTS AND DISCUSSION

In this study, at first, we aimed to design a simple and low-cost method to fabricate PEGDA hydrogel-based nerve guide. The PDMS master mold was prepared via conventional soft lithography process. PDMS prepolymer was mixed with curing reagent in a 10:1 mass ratio. Silicone tubes of the required size were placed radially across the mold and cured in an oven to embed them with PDMS. The experimental set up and fabrication process is depicted in Fig. 1. PEGDA was introduced in between concentrically placed silicone tubes and exposed to UV light source using compact UV exposure system (DYMAX, bluewave 200) for 5 seconds. Once cured, the PEGDA conduit was pushed out as shown in Fig. 2(a), by stretching the PDMS mold

The mold was restored to original position to repeat the steps to fabricate more samples as shown in Fig. 2(b). The procedure followed is very simple and NGCs of any size can be fabricated quickly at very low cost without resorting to expensive lithography processing. The fabricated NGCs with dimensions is represented in Fig. 3(a). The NGCs thus fabricated was coated with parylene (Fig. 3(b)), which is also a biocompatible material, to enhance the stability of the

PEGDA. Parylene deposition was carried out at ambient temperatures with vacuum deposition equipment, which takes place at the molecular level (Lavida, Femto Science, Korea). Since, parylene was applied in a gaseous form, the coating effortlessly penetrates narrow openings, tight areas which provides complete, conformal and uniform deposition. The coated conduit samples were then subjected to hydrolytic swelling test by soaking it at elevated temperature of 37 °C. The NGCs of PEGDA without parylene coating was unstable and there was steep increase in degree of swelling

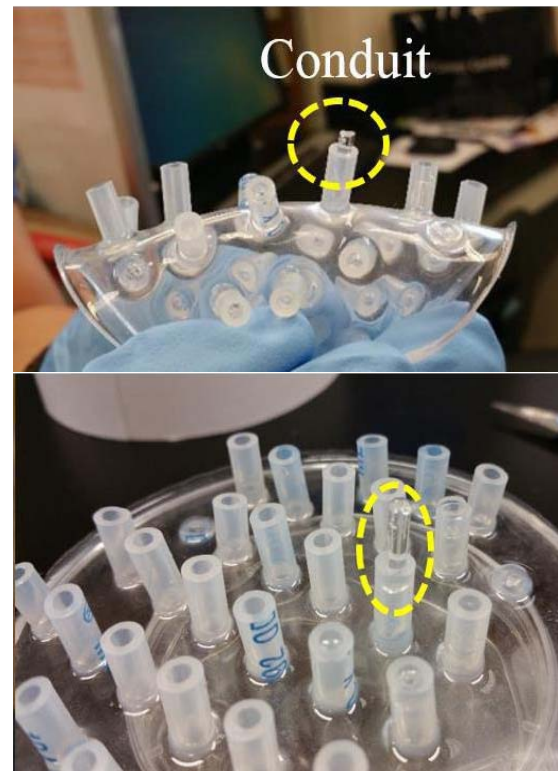


Fig. 2 PDMS master mold (a) master mold bent for the ejection of PEGDA conduit (b) master mold in original position for re-use

(74.42 % after 8 weeks testing). On the other hand, the NGCs of PEGDA coated with parylene was stable, and the

degree of swelling was minimal (1.41 %) over a duration of 8 weeks under soak test as represented in Fig. 3(c). The UV light-curing method that we employed will reduce processing costs, produce high quality stable conduits, and eliminate the

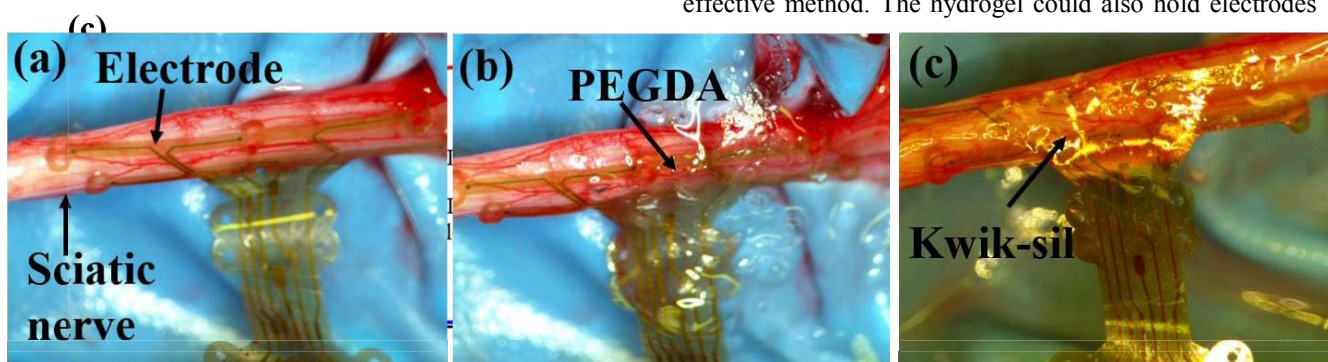
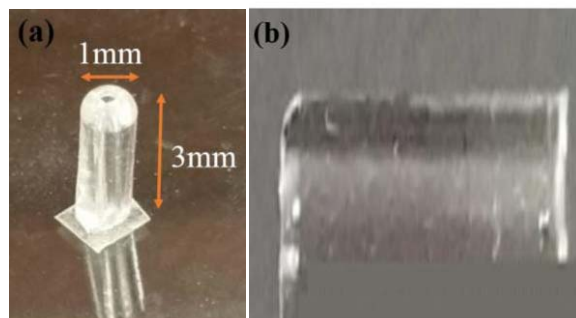


Fig. 4. Strip electrode on sciatic nerve (a) strip electrode positioned (b) cross-linked PEGDA to secure electrode (c) Kwik-sil cured to secure electrode

Fig. 3 PEGDA conduit (a) without parylene coating (b) after 0.3 μm thick parylene coating (c) comparison of degree of swelling at elevated temperature

use of harmful chemicals during the process of fabrication. The fabricated NGCs structure was intact, stable enough and suitable for chronic *in vivo* studies.

Secondly, PEGDA was used as a biogluce to secure different electrodes onto the peripheral nerve. The strip electrode was placed on the sciatic nerve with the electrode contact points properly aligned. The electrode substrate was polyimide, and in this acute experiment, was adhered to the nerve with the application of PEGDA as represented in Fig. 4. *In vivo* Impedance was measured using Intan 2216 chip at 1 kHz frequency, before the application of PEGDA. In the next step PEGDA mixed with photoinitiator at low concentration (0.1 %, V/V) was applied over the electrode, cured with portable UV exposure equipment for 1 minute to form a thin film. Soon after curing, *in vivo* Impedance was measured at 1 kHz frequency. It was evident by moving the rat that the bonding of electrode with nerve and adjoining tissue was sufficiently strong, to keep it in position for longer

duration with cured PEGDA immediately after curing. From the impedance results shown in table 1, it can be observed that the impedance decreased approximately by 1 k Ω with application of PEGDA and curing the same with UV. To establish that the proposed method can be used with different electrode configurations, we tried it with the split ring electrode. The split electrode ring electrode was held in position firmly with application of PEGDA based glue, cured with same parameters as shown in Fig. 5. Similar procedure was repeated with vagus nerve and ribbon electrode and the result is evident from the Fig. 6.

IV. CONCLUSIONS

Here we have successfully employed photosensitive hydrogel, which can be cured within few seconds to fabricate nerve guides quickly with simple and cost-effective method. The hydrogel could also hold electrodes

in position when interfaced with small nerves and enhance electrode contact with the nerve. Light-curing method that we used in both applications has many advantages such as low production costs, high quality product, absence of harmful chemicals. This method can be conveniently applied to secure electrode even with small nerves as other methods are challenging causing nerve injury.

ACKNOWLEDGMENT

This work was supported by grants from National Research Foundation (NRF) CRP project 'Peripheral Nerve Prostheses: A Paradigm Shift in Restoring Dexterous Limb Function' (R-719-000-001-281) and funding under the Invest Northern Ireland and the European Union's INTERREG VA Programme, managed by the Special EU Programmes Body (SEUPB) under the Connected Health Innovation Centre (CHIC) competence center.

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No of trials	1	2	3	4	5	6	7	8	9	10
Impedance in k Ω without PEGDA	4	4.06	4.09	4.08	4.1	4.09	4.07	4	4.07	3.87
Phase angle	-8	-8	-9	-7	-9	-7	-8	-10	-8	-7
Impedance in k Ω with PEGDA	3.06	3.12	3.15	2.98	3.13	3.19	3.22	3.07	3.18	3.03
Phase angle	-10	-10	-9	-8	-8	-8	-9	-8	-9	-10

Table. 1 *In vivo* impedance measurement before and after deposition of PEGDA glue

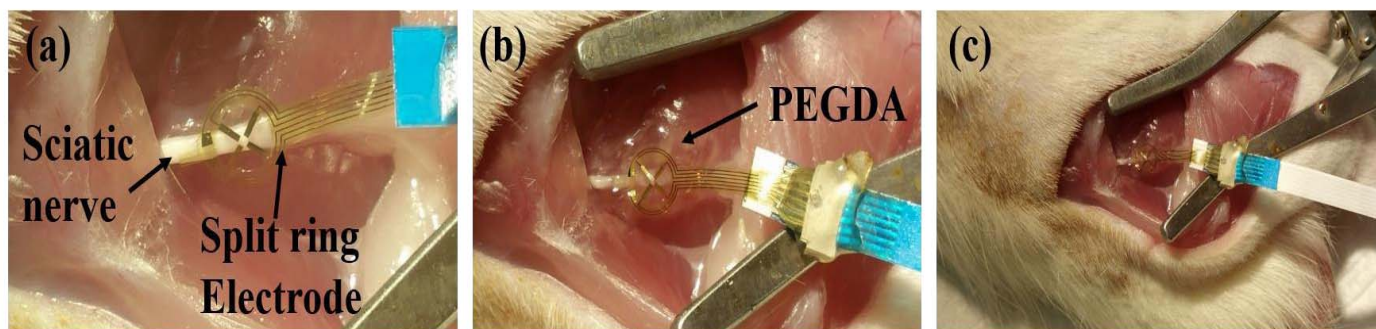


Fig. 5. Split ring electrode on sciatic nerve (a) split ring electrode placed on the nerve (b) cross-linked PEGDA to secure electrode. (c) electrode firmly held by PEGDA

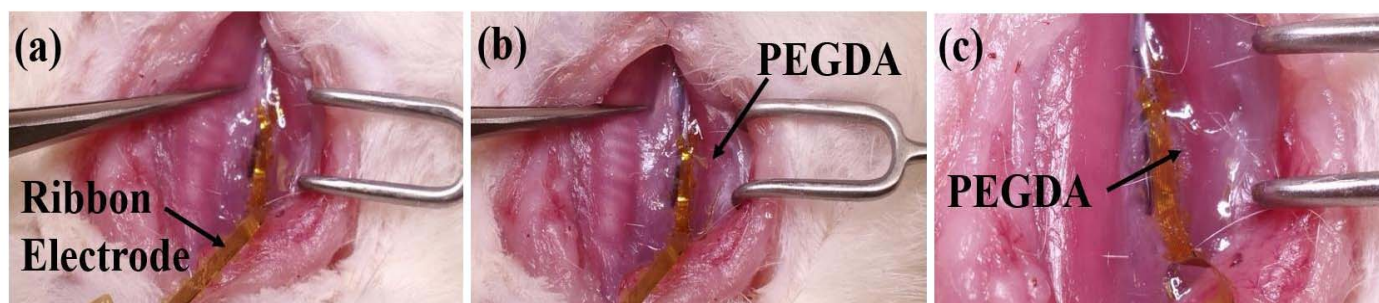


Fig. 6. Ribbon electrode on vagus nerve (a) ribbon electrode placed on the vagus nerve (b) cross-linked PEGDA (c) PEGDA securing electrode firmly with adjoining tissue.

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