Title: *In vivo* biocompatibility of porous and non-porous polypyrrole based trilayered actuators

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Abstract

Introduction: Trilayered polypyrrole (PPy) actuators have high stress density, low modulus and have wide potential biological applications including use in artificial muscles and in limb prosthesis after limb amputation. This article examines the *in vivo* biocompatibility of actuators in muscle using rabbit models. The actuators were specially designed with pores to encourage tissue ingrowth; this study also assessed the effect of such pores on the stability of the actuators *in vivo*.

Method: Trilayered PPy actuators were either laser cut with 150 μ m pores or left pore-less and implanted into rabbit muscle for 3 days, 2 weeks, 4 weeks and 8 weeks and retrieved subsequently for histological analysis. In a second set of experiments, the cut edges of pores in porous actuator strips were further sealed by PPy after laser cutting to further improve its stability *in vivo*. Porous actuators with and without PPy sealing of pore edges were implanted intramuscularly for 4 and 8 weeks and assessed with histology.

Result: Pore-less actuators incited a mild inflammatory response, becoming progressively walled off by a thin layer of fibrous tissue. Porous actuators showed increased PPy fragmentation and delamination with associated greater foreign body response compared to pore-less actuators. The PPy fragmentation was minimized when the pore edges were sealed off by PPy after laser cutting showing less PPy debris.

Conclusion: Laser cutting of the actuators with pores destabilizes the PPy. This can be overcome by sealing the cut edges of the pores with PPy after laser. The findings in this article have implications in future design and manufacturing of PPy actuator for use *in vivo*.

Graphical abstract

Keywords- polypyrrole, biocompatibility, actuator, artificial muscle, tissue engineering, biomaterials.

Introduction:

Limb amputation is a life changing and potentially devastating event for the patient, their families and of great cost to society through health care and on-going losses in productivity. In western societies the major causes of limb amputation include peripheral vascular disease, trauma and tumour resection [1]. With advances in material science and engineering, a range of prosthetic limbs have been devised to restore function to amputees [2, 3]. To satisfy the daily requirements of the user, the prosthesis and its associated actuators must satisfy certain mechanical requirements such as generating high stress, strain, strain rate, and occupy a low volume and show high electro-mechanical coupling efficiency [4-8]. Recently much interest has been focused on polypyrrole (PPy) based actuators that may one day be employed in limb prosthesis [7-13]. PPy is a conductive polymer with favourable electrical properties while maintaining a low modulus. Unlike traditional electric motors, PPy based actuators are capable of generating high stress per unit mass, occupying minimal volume and also optimized for aperiodic activity [7-10]. Furthermore, its low modulus allows for better biological integration and is amenable to further surface modification to enhance its bioactivity [14-17]. In addition to actuation, the PPy component of the actuators may also serve as a platform for electrical stimulation of cells, conductors of biological current between damaged tissues or as a slow delivery device for growth factors and drugs owing to their superior electrical and electroactive properties [18-20].

PPy actuators can be made by sandwiching a platinum coated poly(vinylidene fluoride) (PVDF) membrane between two layers of PPy. Upon application of a voltage difference, one PPy layer undergoes oxidation and the other reduction leading to reciprocal changes in volume causing one side to expand and the other to contract, allowing the actuator to deflect and thus actuate [11-13] (Figure 1). As the final PPy actuator resembles a thin polymer strip, the terms “strip” and “actuator” will be used interchangeably throughout this article. Although PPy actuators have been proposed for use in bio-prosthetics, there are gaps in understanding of the biocompatibility of such devices. A range of studies have examined the biocompatibility of polypyrrole [21, 14, 22-25]; however the biological response to a trilayered PPy actuator remain poorly defined. This study investigates PPy based actuators by implanting into rabbit muscle and characterizing the biological response over time discrete time points. Critically the actuators were also fenestrated with pores to enhance tissue integration and the effect of such pores on the tissue response was also evaluated.

Figure 1: Schematic diagram of the trilayered polypyrrole actuator consisting of a PVDF membrane coated with platinum and sandwiched between two layers of polypyrrole. The polypyrrole layers undergo volume change upon redox reaction deflecting the strip and actuate. Multiple actuators may be assembled into an artificial “muscle fibre” which can be incorporated into a robotic limb.

Methods

Polypyrrole based trilayer actuator

Flexible substrates were prepared by sputter coating platinum (Magnetron sputter coater SC 100MS) on to both sides of a PVDF membrane (Millipore 110mm thickness). p-toluene sulfonic acid (PTSA, 95%) and deionized water were used. Pyrrole (Fluka, 98%) was distilled before use. The polymerization solution contained 0.1 M pyrrole and 0.1 M PTSA mixed in deionized water. Before the reaction commenced, the solution was purged with nitrogen gas for 20 min at room temperature. Polypyrrole was prepared via continuous electrochemical

polymerization methods. Samples were electrochemically deposited with a galvanostatic process at a constant current density of 0.1 mA/cm^2 for 8 hours at room temperature. Stainless steel mesh was used for two counter electrodes and a potentiostat/galvanostat (EG&G Princeton Applied Research Model 363) was used to generate the constant current. The membranes were coated with polypyrrole on both sides. For initial studies assessing the effect of pores on the biocompatibility of the actuator strips, $150\mu\text{m}$ pores spaced by $300\mu\text{m}$ gaps were laser machined into the strips after polypyrrole coating (Universal Laser Systems PLS6MW). For later studies that studied the effect of pore cutting on difference phases of the manufacturing process on polypyrrole breakdown, the pores were either cut before or after polypyrrole polymerization.

Implantation of Polypyrrole actuators

All experiments and treatment of animals were in accordance with the institutional ethics guidelines. New Zealand white rabbits were anaesthetized with Isoflurane gas (1-3%) in oxygen and laid on their back before both hind-limbs were shaved and decontaminated. Under sterile conditions a skin incision was made over the tibialis anterior on the hindlimb. The tibialis anterior muscle was isolated and longitudinal pockets created within the muscle using blunt dissection. The polypyrrole actuator strip was placed into the pocket and the pocket closed with sutures. For the first study aimed at characterizing the biocompatibility of porous PPy strips, one hindlimb of each rabbit was implanted with two non-porous strips (30mm X 5mm) and the other hindlimb was implanted with two porous strips (30mm X 5mm). The non-porous strips were treated as the control. In the second study the effect of polypyrrole coating before or after strip fenestration on polypyrrole breakdown was examined. One hind limb was implanted with two strips that were first coated with PPy and then cut with pores while the other hindlimb was implanted with two strips that were cut with pores then coated with PPy. The strips that were first coated with PPy and then cut with pores was made the control group in the second study. Following recovery from surgery, the rabbits were sacrificed at 4 weeks and 8 weeks post-surgery. A total of three rabbits were used for each time point.

Histology

The tibialis muscles were harvested at 3 days, 2 weeks, 4 weeks and 8 weeks for histological analysis. The tissues were processed and stained by staff at the Biomedical Sciences Histology Facility at the University of Melbourne. The tissues were fixed in 10% neutral buffered formalin for 24 hours and further dehydrated and embedded in paraffin wax (refer to protocol in appendix). $5\mu\text{m}$ paraffin sections were cut from the paraffin

embedded specimens. The sections were stained were either stained with eosin and haematoxylin or Mason's trichrome (refer to protocol in appendix)

Image Analysis

High definition images of the histology slides were obtained using Olympus Olyvia system (Olympus Microscopy, United Kingdom) at 20X magnification and 3 μ m z-stacks were generated. The images were analyzed using FIJI software. Areas of interest were defined by regions 300-500 μ m around the actuator strips, with the total area of interest examined between the different groups was the same. Intensity thresholds were applied so that only the black particles from the polypyrrole were detected, with the total area occupied by the particles calculated using particle analysis. All particles equal to or greater than 1 μ m² were identified. The percentage of the region of interest around each strip occupied by the debris particles was then calculated. The debris value of the two control strips from each rabbit was averaged and all debris values of strips implanted in the same rabbit were normalized to the calculated mean of the control strips.

Statistical Analysis

Each rabbit was implanted with 2 control strips in one hind limb and two strips with treatment of interest in the other leg. A total of three rabbits were used for each time point. Each strip was treated as a single n and the values were normalized to the average of the two strips on the control limb. Graphpad Prism (Version 5.0) was used to perform the Student's paired and unpaired t-test and a one-way ANOVA with Bonferroni's post-hoc test, to assess statistical significance between treatments.

Results

Comparison of porous and non-porous PPy actuators biocompatibility

At 3 days after implantation, fibrin and inflammatory cells surrounded both porous and non-porous strips (Figure 2). Porous strips with PPy at the cut edges of the pores partially detached (Figure 2 A and B) indicating PPy coating instability. By 14 days, the fibrinous exudate undergoes granulomatous change, with the strips directly surrounded by a layer of giant cells (Figure 3). Between the giant cells and the surrounding muscle lies a zone of granulation tissue. In porous strips, significant tissue ingrowth into the pores of the actuator was noted (Figure 3 A and B). Polypyrrole debris was found around porous strips while non-porous strips show minimal breakdown (Figure 3 C and D). By 4 weeks after implantation, the granulation tissue continued to organize into collagen tissue, encapsulating the PPy strips (Figure 4). Breakdown of PPy coating continued in porous PPy strips with more PPy debris embedded in the collagenous tissue around the strip (Figure 4 A). Non-porous PPy strips remained stable in muscle with minimal signs of PPy coating delamination. (Figure 4 B). There was also marked fat infiltration into the collagenous tissue around the strips (Figure 4 A). By 8 weeks after implantation, there was further breakdown of PPy debris (Figure 5 A and B). Additionally, the granulomatous tissue layer continued to remodel and there was progressive fat atrophy of the muscle surrounding the strip. (Figure 5 A-C). Again, minimal breakdown of PPy was noted in non-porous strips (Figure 5 C).

PPy delamination in porous and non-porous PPy actuators

Given the marked difference in PPy breakdown between porous and non-porous Ppy strips, the amount of PPy debris in the tissue directly opposing the strip was analysed with image analysis (Figure 6). At two weeks after implantation there was a statistically non-significant trend towards more PPy breakdown in porous strips compared to non-porous strips (Figure 6 A). By 4 and 8 weeks the difference between the two treatment arms had further widened, with porous strips showing 34.7 times ($p<0.01$) and 18.1 times ($p<0.01$) more PPy debris compared to non-porous strips at 4 weeks and 8 weeks respectively (Figure 6 C and E). There was no significant difference in the area of tissue that was analysed for Ppy debris between the porous and the non-porous strip groups at all time points (Figure 6 B, D, F).

Up until this point, all the data presented on the actuators relate to actuator strips that were first coated with polypyrrole then cut to form pores. One of the proposed mechanisms underlying PPy coating instability in these porous strips was that the interface between the PPy and the platinum was exposed by the cutting of pores in the strips. The exposed edge allowed fluid to seep into the interface between PPy and platinum thus delaminating the PPy off the platinum. To further test this hypothesis, holes were either cut into the Pt coated PVDF membranes before PPy was polymerized on it or after the PPy polymerization had completed. The two types of strips were implanted into rabbit muscle for 4 and 8 weeks and the level of PPy debris was compared (Figure 7). Breakdown was present in both treatments, however at 4 weeks there was a trend towards more PPy debris in muscles with porous strips that were PPy coated then cut (Figure 7 A). This was not due to any difference in the area of tissue examined for debris (Figure 7 B). By 8 weeks, strips that were cut then coated were markedly more stable, with PPy debris reduced by as much as 79% compared to strips coated then cut ($p < 0.01$) (Figure 7 C). Again this was not due to any difference in area of tissue analysed (Figure 7 D).

3 Days

A

Mason's Trichrome

B

H&E

C

Mason's Trichrome

D

H&E

Figure 2: Mason's trichrome (A and C) and H&E stains (B and D) of rabbit muscles with porous (A-B) and non-porous (C-D) PPy actuator strips 3 days post implantation.

Figure 3: Mason's trichrome and H&E stains of rabbit muscles with porous (A-C) and non-porous (D) PPy actuator strips 14 days post implantation. Note the breakdown of PPy in porous strips (C) , contrasting with the stability of the PPy layer in nonporous strips (D).

4 Weeks

Porous strips

A

Pore-less strips

B

Figure 4: Mason's trichrome stains of rabbit muscles with porous (A) and non-porous (B) PPy actuator strips 4 weeks post implantation.

8 Weeks

Figure **Error! No text of specified style in document.**: Mason's trichrome and H&E stains of rabbit muscles with porous (A-B) and non-porous (C) PPy actuator strips 8 weeks post implantation.

Figure 6: PPy breakdown in porous and non-porous PPy strip actuators. Histology slides of muscle specimens from 2 weeks (A-B), 4 weeks (C-D) and 8 weeks (E-F) were analysed for PPy debris using image analysis. A zone of tissue 300-500um from the strip was isolated and the percentage area of this zone occupied by PPy debris calculated (A, C and E). The total area of tissue around porous and non-porous strips that was analysed

was compared to ensure no bias in analysis (B, D and F). Data from 12 strips (6 porous, 6 non porous) implanted intramuscularly into 3 rabbits per time point. Column and error bars represent mean $\pm$ SEM. ** - $p < 0.01$, unpaired student t-test

Figure 7: PPY breakdown in porous strips that were coated before holes were cut (control) and those that were cut with pores before PPY coating. PPY debris level (A and C) and the total area that had been examined for debris presence (B and D) were compared. Data from 12 strips (6 cut before coat, 6 coat before cut) implanted intramuscularly into 3 rabbits per time point. Column and error bars represent mean $\pm$ SEM. ** - $p < 0.01$, unpaired student t-test)

Discussion

Polypyrrole based trilayered actuators potentially provide a light and efficient alternative to traditional electric motors for mobilising limb prostheses. In this study we examined the biocompatibility of these actuator strips. Furthermore we engineered pores into the strips to promote tissue integration and assessed the impact of these pores on the overall stability of the polypyrrole coating on the actuators.

As expected there was a foreign body response to the implantation of the actuator strip. The strip was first surrounded by fibrin, blood and inflammatory cells. Over time the exudate began to organize and form granulomatous tissue. Giant cells enveloped the strips and the surrounding tissue was invaded by new vessels and macrophages. By 4 to 8 weeks, the tissue progressively became more collagenous and less cellular forming a layer of collagen around the actuator strip. Similar results have been reported previously with polypyrrole coated electrodes implanted both subcutaneously and in the CNS of animals. The tissue responses were comparable and sometimes less than common biological scaffolds currently used for implantation such as Teflon and PLGA [14, 22-24, 21, 25]. However, most studies have not examined the stability of polypyrrole *in vivo*. Our results show that the presence of pores in the polypyrrole strip destabilizes the coating causing the polypyrrole to delaminate from the platinum substrate. Previous studies that have examined the stability of polypyrrole coatings have been conducted *in vitro* in simulated physiological solutions [26-28]. Most cases of polypyrrole delamination occur after chronic electrical stimulation [26-28]. It was postulated that the redox reactions secondary to stimulation lead to cyclical volume changes to the polypyrrole predisposing it to peel off from its substrate [27]. Other authors have attributed the instability to the significant levels of α - β' coupling in its chemical structure leading to defect sites on its polymer backbone [29, 30]. The defect sites are thought to be primary sites of breakdown in response to oxidation. The propensity for delamination has been linked to the thickness of the conductive polymer coating [31]. However, these explanations do not apply to our setting as the non-porous polypyrrole strip was relatively stable through the experiment. The key difference between the two treatment arms was the presence of pores in the group that showed delamination. Furthermore, signs of delamination at the edges of the pores were visible as early as 3 days after implantation of the strips. The pores were likely related to the delamination mechanism. It was thought that by cutting pores in the strips, the interface between the polypyrrole and the platinum was exposed at the edges of the pores. Overtime, biological fluids, cells will infiltrate between the layers delaminating the polypyrrole. This is supported by the finding that

sealing the pore edges by first cutting the pores and then coating with polypyrrole significantly reduced the amount of polypyrrole debris.

There are some limitations to our study. Firstly the quantification of polypyrrole debris was achieved through image analysis. Therefore, the measure is subject to sampling bias. Still all attempts were made to sample the same area of tissue for both treatment arms. Secondly, during the image analysis process, the area occupied by polypyrrole debris was distinguished from surrounding regions by its black pigment. However sometimes small amounts of dark coloured cell nuclei may also have been detected by the computer algorithm and incorporated into the debris area measure. However the amount of dark nuclei with intensity levels approaching black is small for each slide image and is unlikely going to impact the large differences noted between the treatment arms.

Conclusion:

Fenestration of PPy actuators promotes a heightened foreign body response compared to non-porous strips. This was likely mediated by seepage of tissue fluid into planes between the PPy and the underlying platinum membrane at the cut edges of the pores thus destabilizing and delaminating the PPy layer. This can be averted by sealing the cut edges of the pores with PPy. Our results have direct implications on the future design and development of PPy actuators whereby pores should be avoided in the design of the actuators strip. In situations where fenestration to the actuator is required, a further process of polypyrrole coating should be attempted after pores are cut.

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References

1. Dillingham TR, Pezzin LE, MacKenzie EJ. Limb amputation and limb deficiency: epidemiology and recent trends in the United States. *Southern medical journal*. 2002;95(8):875-83.
2. Schultz AE, Kuiken TA. Neural interfaces for control of upper limb prostheses: the state of the art and future possibilities. *PM & R : the journal of injury, function, and rehabilitation*. 2011;3(1):55-67.
doi:10.1016/j.pmrj.2010.06.016.
3. Carey SL, Lura DJ, Highsmith MJ. Differences in myoelectric and body-powered upper-limb prostheses: Systematic literature review. *Journal of rehabilitation research and development*. 2015;52(3):247-62.
doi:10.1682/JRRD.2014.08.0192.
4. Mirfakhrai T, Madden JDW, Baughman RH. Polymer artificial muscles. *Materials Today*. 2007;10(4):30-8.
doi:[http://dx.doi.org/10.1016/S1369-7021\(07\)70048-2](http://dx.doi.org/10.1016/S1369-7021(07)70048-2).
5. Hollerbach JM, Hunter IW, Ballantyne J. A comparative analysis of actuator technologies for robotics. In: Khatib O, Craig JJ, Lozano-Pérez T, editors. *The robotics review 2*. MIT Press 1992. p. 299-342.
6. Samatham R, Kim KJ, Dogruer D, Choi HR, Konyo M, Madden JD et al. Active Polymers: An Overview
In: Kim KJ, Tadokoro S, editors. *Electroactive Polymers for Robotic Applications Artificial Muscles and Sensors*. 1 ed.: Springer-Verlag London; 2007. p. 1-36.
7. Madden JD. Polypyrrole Actuators: Properties and Initial Applications. In: Kim KJ, Tadokoro S, editors. *Electroactive Polymers for Robotic Applications: Artificial Muscles and Sensors*. London: Springer London; 2007. p. 121-52.
8. Madden JDW, Schmid B, Hechinger M, Lafontaine SR, Madden PGA, Hover FS et al. Application of polypyrrole actuators: feasibility of variable camber foils. *IEEE Journal of Oceanic Engineering*. 2004;29(3):738-49. doi:10.1109/joe.2004.833128.
9. Madden JD, Cush RA, Kanigan TS, Hunter IW. Fast contracting polypyrrole actuators. *Synthetic Metals*. 2000;113(1-2):185-92. doi:[http://dx.doi.org/10.1016/S0379-6779\(00\)00195-8](http://dx.doi.org/10.1016/S0379-6779(00)00195-8).
10. Hara S, Zama T, Takashima W, Kaneto K. Artificial Muscles Based on Polypyrrole Actuators with Large Strain and Stress Induced Electrically. *Polym J*. 2004;36(2):151-61. doi:10.1295/polymj.36.151.
11. Wu Y, Alici G, Spinks GM, Wallace GG. Fast trilayer polypyrrole bending actuators for high speed applications. *Synthetic Metals*. 2006;156(16-17):1017-22. doi:<http://dx.doi.org/10.1016/j.synthmet.2006.06.022>.

12. John SW, Alici G, Cook CD. Inversion-Based Feedforward Control of Polypyrrole Trilayer Bender Actuators. *IEEE/ASME Transactions on Mechatronics*. 2010;15(1):149-56. doi:10.1109/tmech.2009.2020732.
13. Kiefer R, Mandviwalla X, Archer R, Tjahyono SS, Wang H, MacDonald B et al., editors. The application of polypyrrole trilayer actuators in microfluidics and robotics 2008.
14. Cui X, Wiler J, Dzaman M, Altschuler RA, Martin DC. In vivo studies of polypyrrole/peptide coated neural probes. *Biomaterials*. 2003;24(5):777-87.
15. Cui X, Lee VA, Raphael Y, Wiler JA, Hetke JF, Anderson DJ et al. Surface modification of neural recording electrodes with conducting polymer/biomolecule blends. *Journal of biomedical materials research*. 2001;56(2):261-72.
16. Stauffer WR, Cui XT. Polypyrrole doped with 2 peptide sequences from laminin. *Biomaterials*. 2006;27(11):2405-13. doi:10.1016/j.biomaterials.2005.10.024.
17. Meng S, Rouabhia M, Shi G, Zhang Z. Heparin dopant increases the electrical stability, cell adhesion, and growth of conducting polypyrrole/poly(L,L-lactide) composites. *Journal of biomedical materials research Part A*. 2008;87(2):332-44. doi:10.1002/jbm.a.31735.
18. Stewart E, Kobayashi NR, Higgins MJ, Quigley AF, Jamali S, Moulton SE et al. Electrical stimulation using conductive polymer polypyrrole promotes differentiation of human neural stem cells: a biocompatible platform for translational neural tissue engineering. *Tissue engineering Part C, Methods*. 2015;21(4):385-93. doi:10.1089/ten.TEC.2014.0338.
19. Thompson BC, Moulton SE, Ding J, Richardson R, Cameron A, O'Leary S et al. Optimising the incorporation and release of a neurotrophic factor using conducting polypyrrole. *Journal of Controlled Release*. 2006;116(3):285-94. doi:<http://dx.doi.org/10.1016/j.jconrel.2006.09.004>.
20. Kim D-H, Martin DC. Sustained release of dexamethasone from hydrophilic matrices using PLGA nanoparticles for neural drug delivery. *Biomaterials*. 2006;27(15):3031-7. doi:<http://dx.doi.org/10.1016/j.biomaterials.2005.12.021>.
21. Wang Z, Roberge C, Dao LH, Wan Y, Shi G, Rouabhia M et al. In vivo evaluation of a novel electrically conductive polypyrrole/poly(D,L-lactide) composite and polypyrrole-coated poly(D,L-lactide-co-glycolide) membranes. *Journal of biomedical materials research Part A*. 2004;70(1):28-38. doi:10.1002/jbm.a.30047.
22. Schmidt CE, Shastri VR, Vacanti JP, Langer R. Stimulation of neurite outgrowth using an electrically conducting polymer. *Proceedings of the National Academy of Sciences*. 1997;94(17):8948-53.
23. George PM, Lyckman AW, LaVan DA, Hegde A, Leung Y, Avasare R et al. Fabrication and biocompatibility of polypyrrole implants suitable for neural prosthetics. *Biomaterials*. 2005;26(17):3511-9. doi:10.1016/j.biomaterials.2004.09.037.

24. Wang X, Gu X, Yuan C, Chen S, Zhang P, Zhang T et al. Evaluation of biocompatibility of polypyrrole in vitro and in vivo. *Journal of biomedical materials research Part A*. 2004;68(3):411-22. doi:10.1002/jbm.a.20065.
25. Richardson RT, Wise AK, Thompson BC, Flynn BO, Atkinson PJ, Fretwell NJ et al. Polypyrrole-coated electrodes for the delivery of charge and neurotrophins to cochlear neurons. *Biomaterials*. 2009;30(13):2614-24. doi:10.1016/j.biomaterials.2009.01.015.
26. Jiang X, Marois Y, Traore A, Tessier D, Dao LH, Guidoin R et al. Tissue reaction to polypyrrole-coated polyester fabrics: an in vivo study in rats. *Tissue engineering*. 2002;8(4):635-47. doi:10.1089/107632702760240553.
27. Wadhwa R, Lagenaur CF, Cui XT. Electrochemically controlled release of dexamethasone from conducting polymer polypyrrole coated electrode. *Journal of controlled release : official journal of the Controlled Release Society*. 2006;110(3):531-41. doi:10.1016/j.jconrel.2005.10.027.
28. Thompson BC, Moulton SE, Ding J, Richardson R, Cameron A, O'Leary S et al. Optimising the incorporation and release of a neurotrophic factor using conducting polypyrrole. *Journal of controlled release : official journal of the Controlled Release Society*. 2006;116(3):285-94. doi:10.1016/j.jconrel.2006.09.004.
29. Schlenoff JB, Xu H. Evolution of Physical and Electrochemical Properties of Polypyrrole during Extended Oxidation. *Journal of The Electrochemical Society*. 1992;139(9):2397-401. doi:10.1149/1.2221238.
30. Pfluger P, Street GB. Chemical, electronic, and structural properties of conducting heterocyclic polymers: A view by XPS. *The Journal of Chemical Physics*. 1984;80(1):544-53. doi:doi:<http://dx.doi.org/10.1063/1.446428>.
31. Cui XT, Zhou DD. Poly (3,4-ethylenedioxythiophene) for chronic neural stimulation. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society*. 2007;15(4):502-8. doi:10.1109/TNSRE.2007.909811.

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Polypyrrole based actuator

Implanted into animal muscle

Tissue integration and biocompatibility