Universitat de Girona
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Treball final de grau

Estudi: Grau en Enginyeria Biomèdica

Títol: Two-photon lithography for fabrication of implantable drug delivery devices

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3 out of 5 people will be diagnosed with cancer at some point during their lifetimes and around a third of them will die because of it. With more than 12 000 new cases each year in the UK and doubling the numbers in the States, brain tumours are a common disease that directly impacts patients' life. Furthermore, only 12% of patients survive for five or more years after being diagnosed.

A combination of chemotherapy, radiotherapy and, if possible, surgical resection have been traditional methods for cancer treatment. Unfortunately, some treatments such as in brain cancer are deadlier since we are not able to administrate the drug effectively. Chemotherapy has limitations such as the blood-brain barrier, which plays a pivotal role in protecting the central nervous system from toxic substances but also significantly reduces the amount of cancer drugs that can be delivered. A bad vascularization of solid brain tumours further complicates the delivery of therapeutically relevant drug doses. Thus, a multitude of technologies have been developed to overcome those limitations; binding molecules to nanoparticles or using ultrasounds to temporarily disrupt the barrier. A different approach is avoiding the barrier by delivering cancer drugs directly into tumours.

This project was undertaken in attempt to improve the efficacy of the drug delivery while avoiding systemic toxicity, designing a novel implantable drug delivery platform for iontophoretic brain cancer therapy.

3D fabrication is fast becoming key instrument in the medical field. Thus, we explored microfabrication of an implantable drug delivery device, concretely using direct laser writing to electrostatically deliver charged cancer drugs into brain tumours, technology which is called iontophoresis – basically relies on the motion of ions in electric fields. This technology avoids pressure-related problems, such as drug reflux and brain oedema formation, encountered with convection enhanced delivery by solely relying on the motion of ions in electric fields. The reason for the interest in iontophoresis is that this technique is very versatile allowing to deliver substances into tissue which are usually impermeable. Additionally, it opens up the possibility to deliver drugs in a targeted fashion directly into the desired tissue instead of administering it systemically which reduces off-target toxicity and allows higher delivery rates than when relying solely on passive diffusion of the drug.

Our starting point was a very basic structure, a MVP; device with U-shape microfluidic channels. Once it fulfilled our requirements, we improved each feature, one at a time, until we achieved the final prototype: a 0.9 diameter and 1.5mm height device with helix-shape microfluidic channels, which allowed us to have more surface area and, as a result, increase the solution

volume inside the device, 0.02mm diameter circular pores, agarose based membrane and room for an electrode to be placed in the middle. This methodology helped us solve the problems faster. Thus, it proved worth using a continuous improvement method instead of trying multiple things at once. We can see the first and final prototype in the following figures:

Figure 1: first prototype

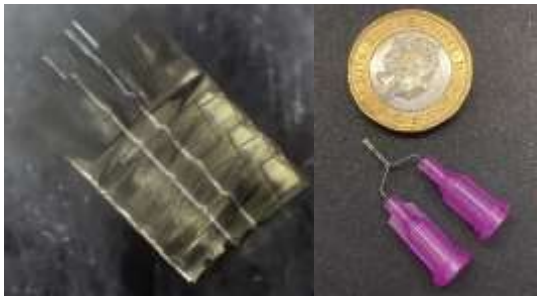

Figure 2: final prototype

We did not quantify the amount of cisplatin that can be delivered from the solution since the mass spectroscopy machine was broken. However, we were able to see there was a difference between the amount of dye delivered before and after the coating of the device in the membrane. To probe that we injected 20ml dye (50ml/molar methanol blue) in the needle and afterwards, we put the device inside a UV-transparent cuvette filled with 50ml of 100m/molar NaCl and waited for 10min seeing a decrease in the delivered dye after coating.

Considerably more work will need to be done to determine the utility of the current membrane in terms of diffusion, convection and drug delivery.

Nanoscribe, a high-performance laser lithography system for rapid prototyping and wafer-scale batch production was used in this project. This 3D printing machine is based in two-photon polymerization, also called direct laser writing, which is a high-resolution 3D photolithography technique that relies on the local solidification of a photoresist at the focus of a laser beam to “draw” structures with feature sizes down to a 100nm. We can confirm that rapid prototyping allowed the fabrication of sub-millimetre-sized brain implants for iontophoretic cancer drug delivery and also that two-photon lithography has efficient resolution for the fabrication of these microfluidic devices which can be interfaced with macroscopic pressure controllers. Thus, we were able to develop of a novel implantable drug delivery platform for brain cancer therapy.

Overall, this study strengthens the idea that very precise microdevices can be fabricated using Nanoscribe while meeting the biocompatibility criteria, which opens the door to future applications in other areas such as neurological diseases and other cancer treatments.