PRAMIPEXOLE-CONTAINING DISSOLVING MICROARRAY PATCHES FOR THE TREATMENT OF PARKINSON'S DISEASE

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Background: Parkinson's disease is a debilitating neurodegenerative disease that predominantly affects dopamine-producing neurones within the brain [1]. Pramipexole (PRA) is a non-ergot dopamine agonist which increases dopamine neurotransmission, restoring balance and alleviating symptoms, such as rigidity and tremor. PRA is currently available in tablet form with a maximum daily dose of 3.3 mg (expressed in terms of PRA base) and a bioavailability of 90%. However, due to the disease, patients usually experience dysphagia and gut motility issues, rendering oral preparations undesirable. Dissolving microneedle array patches (MAPs) can alleviate these problems with an additional benefit of tailoring the drug release kinetics from the MAP by altering the polymer and drug form. The aim of this research was to develop a PRA salt containing-MAP composed of rapidly dissolving, biocompatible, polymers for immediate release of PRA. A second MAP containing PRA base, a more hydrophobic form, was formulated with a biodegradable polymer, poly(lactic-co-glycolic acid) (PLGA), to form implantable tips with the aim of sustaining PRA release.

Methods: A bilayer-casting technique was employed to formulate PRA salt dissolving MAPs. The first layer was composed of PRA salt, poly(vinylpyrrolidone) (PVP) and poly(vinyl alcohol) (PVA). The baseplate layer contained PVP, PVA and glycerol. A similar approach was used to formulate PRA-PLGA MAPs, with the first layer comprising PRA base and PLGA (LA:GA 75:25, viscosity 0.8-1.0 dL/g) dissolved in DMSO. Nile red was added to the solution for staining purposes. Following drying, a second PRA-PLGA layer was cast on several MAPs, again, the baseplate layer contained PVP, PVA and glycerol. This enabled comparison between MAPs with one or two PRA-PLGA casting layers. For both MAP formulations, an excess of the gel/solution was cast on the microneedle mould which consisted of 600 pyramidal needles per 0.75 cm^2, with each needle having a height of 750 µM. The MAPs were characterised in terms of their mechanical strength and insertion efficiency into eight layers of Parafilm M®, which replicated the thickness of skin [2].

Results: MAPs formed from casting aqueous gels containing 10% and 20% PRA salt, had a drug content of 0.70 ± 0.05 mg and 1.40 ± 0.19 mg, respectively, expressed in terms of PRA base, demonstrating uniform drug distribution within the needle tips. After the needles were pierced through Parafilm M® it was found that the 10% salt MAPs were stronger than the 20% MAPs, reflected by a percentage needle height reduction of 2.34 ± 2.91% and 16.49 ± 8.80%, respectively. Interestingly, 75% of needles in both formulations were capable of penetrating through the 2nd layer of Parafilm M® equating to a skin depth of 252 µM. Uniform PRA-PLGA MAPs were formulated with PLGA concentrated in the needle tips. The height of the PLGA tips for one and two layer castings was 239.92 ± 15.62 µM and 298.53 ± 17.79 µM, respectively. This represents 32.0% and 39.8% of the total needle height, respectively.

Conclusions: Uniform PRA base and salt MAPs have been successfully formulated. Future work will focus on *in vitro* permeation of PRA salt as well as permeation and skin deposition of PRA base using Franz cells.

References:[1] Triarhou, L.C., Introduction, in Dopaminergic Neuron Transplantation in the Weaver Mouse Model of Parkinson's Disease. 2002, Springer US: Boston, MA. p. 1-14.

[2] Larrañeta, E., et al., A proposed model membrane and test method for microneedle insertion studies*. Int J Pharm*, 2014. **472**(1-2): p. 65-73.