THE DEVELOPMENT OF MICRONEEDLES CONTAINING IMIQUIMOD FOR LOCALISED DRUG DELIVERY TO A RESECTION CAVITY OF GLIOBLASTOMA

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Background:
Glioblastoma multiforme (GBM) is one of the most aggressive and malignant form of primary brain tumors and despite medical advancements, the persistence recurrence of GBMs post-resection remains a challenge, urging innovative approaches to complement existing standard therapeutic strategies, such as temozolomide and radiotherapy. GBMs create an immunosuppressive microenvironment therefore, immunotherapy is a promising avenue which can target tumour cells and their microenvironment through activation of the immune system. Localized delivery of immunomodulators is compelling as it offers to overcome the blood-brain barrier (BBB) and enhance therapeutic efficacy while minimizing systemic side-effects. Thus, fabricating polymeric microneedle (MN) patches, which allow anchoring within a resection cavity, offer benefits such as precise targeting of therapeutic agents, reduced invasiveness, and improved patient compliance, whilst also facilitating sustained release and enhancing therapeutic outcomes. The aim of this study is to develop and characterize an immunomodulator based therapeutic, a microneedle patch containing imiquimod, that can be delivered locally following glioblastoma resection to prevent tumor recurrence as an adjuvant to standard care.

Methods:
A two-step casting method was used to manufacture the microneedle patches. The three polymers tested as the needle layer include polyvinyl alcohol (PVA), vinylpyrrolidone/vinyl acetate (PVP/VA), and poly(N-acryloylmorpholine (PNAM). Also, two different backing layers tested were carboxymethyl cellulose (CMC) and PVA. The needles on the MN patches were characterized using an optical microscope, which allowed for needle shaft length and shaft width measurements . Also, a texture analyzer was used to measure the fracture force (N) of the MN patches. Further, the effect of room temperature drying versus oven drying on MN formation was investigated

Results:
Amongst the three polymers, PVA was observed to have the strongest fracture force, 2.46 ± 0.08 N, in comparison to PVP/VA, 1.0 ± 0.06 N and PNAM, 1.0 ± 0.10 N. It is reasonable to assume that PVP/VA and PNAM will create more suitable MNs for brain application as they are less likely to cause damage to the delicate brain tissue in comparison with PVA. Additionally, through the microscopy images alone, it is evident that the oven dried MN patches are more well formed in comparison to the room temperature dried MN patches, and this was further emphasized through the comparison of MN shaft width and needle length to the master mold. Of the two backing layers, CMC and PVA, it can be considered that CMC is more suitable in the brain, as the fracture force for PVP/VA increased from 1.0 ± 0.06 N (CMC backing layer) to 2.2 ± 0.07 N (PVA backing layer); also, most importantly CMC has been shown to have adhere well to brain tissue to the resection site .

Conclusions:
This experiment allowed for the opportunity to advance our understanding in development of a microneedle-based delivery system for imiquimod to brain tumor resection site which ultimately could improve patient prognosis, glioblastoma recurrence, and long-tern survival rates.