Exploring formulations for imiquimod patches for the treatment of glioblastoma

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Background: Glioblastoma is a cancer that arises from glial cell mutations in the brain and was the most common type of brain cancer between 1995-2017. It also has a low survival rate with 5% of patients surviving with a median survival of 14-24 months once treatment begins. Systemic side effects from chemotherapy and radiation, especially post surgically, make both recovery and the overall treatment processes difficult for patients. However, if a more direct method of delivering drugs to the brain, bypassing the blood brain barrier are developed, patients could experience fewer negative effects. The aim is to explore formulations for patches containing 5mg/ml imiquimod for application on post-surgery glioblastoma resection site.

Methods: First a stabilizing solution was formulated to function as a stabilising solution for the Imiquimod suspension. Excipients (CMC, Tween 80, Glycerol and distilled water) were added at various concentrations into separate bottles and vortexed for 1 minute. Batches 1-3 were sonicated for 1 hour, whilst all the other batches were immediately placed on a hot plate at 60 °C with a magnetic stirrer until completely dissolved. Imiquimod was weighed into separate bottles to create a final suspension at 5 mg/ml. The solvent bottle was taken off the hot plate and solvent was added to the Imiquimod bottle before vertexing for 1 minute. They were returned to the magnetic stirrer at 40°C for one hour, sonicated for 30 minutes and degassed for 20 Minutes. 200 microliters of suspension was pipetted into square silicone molds. The batches where split; some underwent centrifugation for 10 minutes whilst the rest were immediately placed in the vacuum without centrifugation. They were dried for 3 days, demolded placed in clean glass bottles and kept in a vacuum with silica gel.

Results: The formulations that used higher concentrations of CMC were very viscous, especially whilst cold leading to uneven drug dispersal. Patches of batch 1 (5% CMC) were discarded as a result. However, although at lower concentrations the drug was easier to suspend, the drug tended to fall out of suspension quickly leading to deposition at the bottom of the patch when drying. Furthermore, both batch 3A and B with 1% CMC crumbled whilst demolding and were discarded. When centrifuged the solution separated and formed a drug layer above the solution. Some patches did not dry flat patches but instead had raised 'walls' around the perimeter and this created anomalous results. There were also anomalous results due to imprecise pipetting. There was uneven drying of the patches that left the middle area especially prone to thinning. It is not yet clear why the thinning occurred. The 3-point bend test showed the most variation in properties when it came to the concentration of CMC used in the patches where 3% had the lowest hardness and toughness but the highest brittleness. Whilst 5% CMC had the highest average hardness and toughness and the lowest brittleness. None of the other changes in Tween or glycerol concentrations made a notable change in the results. In UV spectrometry, the calibration curve was created using Imiquimod free base and 0.1M HCL. Then batches 4-6 where each dissolved in 20ml of distilled water, then split where half were diluted further to a ratio of 1:1 suspension to water and all batches were analysed. There was a high average recovery (mean 84%) of the imiquimod in the patches that further diluted to increase sensitivity.

Conclusions: Overall, despite the success of formulating a patch with a high retention of drug, further formulation is required to create a more optimum patch with better physical properties such as more flexibility and lower brittleness. In the future, the patches could be used on living cancer cells in Vivo or in organ models like rat brains.