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| **Optimising the formulation of pectin microneedles for mesenchymal cell delivery for the treatment of traumatic brain injury.** |
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| **Background:** Low-methoxylated pectin forms hydrogels in the presence of calcium ions. Hence, the goal of this study was to explore pectin/calcium carbonate formulations for fabricating hydrogel forming microneedle patches that have the ability to penetrate brain tissues and hence the potential to deliver mesenchymal stem cells locally for the treatment of traumatic brain injury (TBI) in addition to existing surgical method. Additionally, this is useful in delivering higher concentration of mesenchymal stem cells to treat traumatic brain injury, where this aspect requires more exploration. |
| **Methods:** 4 pectin grades, CU-701, CU-L, LM-102, and LM-104 with different degrees of esterification (DE) and degree of methylation (DM) were studied. Calcium carbonate was chosen as the pectin cross-linker in the study as it exhibits slow-gelling properties at concentrations ranging from 15mM to 70mM.  Gelation screenings were conducted using tabletop inversion. Pectin/calcium carbonate formulations were then selected to fabricate microneedle arrays using a two-step polymer casting process using PDMS moulds and then air drying. Microneedle dimensions once demoulded were determined using an optical microscope. The mechanical strength of microneedles was assessed by a fracture force test using a texture analyser. |
| **Results:** Gelation screening of 1%, 2% and 4% w/v via tabletop inversion showed that as the concentration of pectin increases, the lower the calcium carbonate concentration was needed to form a hydrogel. A final gelation screen demonstrated a concentration of 15 mM with 4% w/v pectin was optimum for all the pectin grades. Essentially, this was chosen to progress to microneedle fabrication, as the concentration of calcium ions added should be as close as possible to the brain environment where extracellular calcium concentration ranges from 1.5 - 2.0 mM.  Dimensions of the microneedle arrays were then measured and compared with the polydimethylsiloxane (PDMS) mould used to cast the microneedles. The microneedle tip-to-base height of the PDMS mould used was 1000 𝜇m. The mean tip-to-base height of microneedles formed across all concentrations and grades was 912.31 ± 56.12 𝜇m (mean ± SD), where the standard error of the mean was minimal with a value of 0.88%.  There is no existing data in respect of the force required to penetrate the brain tissue successfully. Nevertheless, there is a large amount of data on the strength required for the successful insertion of microneedles into the skin, which is typically less than 0.098 N/microneedle. According to the results obtained, all the microneedles have a fracture force greater than 0.098 N/microneedle. Hence, all the microneedles fabricated may penetrate the brain effectively without breaking. Generally, when a higher concentration of calcium carbonate was used, the fracture force was greater for all pectin grades. |
| **Conclusions:** Overall, as the concentration of pectin and calcium carbonate increases, the gel strength increases for all pectin grades. Most importantly, we can conclude that the 4% w/v pectin with 15 mM CaCO3 formulation can be fabricated as a microneedle patch with the potential to deliver mesenchymal stem cells for the treatment of traumatic brain injury. |