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| **Solid implants made using solid drug nanoparticles: from proof of concept to *in vivo* studies.** |
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| **Background:** The development of antiretroviral therapies (ARTs) has made HIV a lifelong manageable condition. These therapies involve taking multiple HIV therapeutics to reduce the viral load in the patient to <50 copies/mL, rendering the virus supressed. Poor adherence to therapeutic regimen can have a significant impact on the effectiveness of treatment, potentially leading to treatment failure. Efforts to decrease dosage frequency and improve adherence have been made, with long-acting antiretroviral therapies (LA-ARTs) being developed. Here we demonstrated the production of solid, homogeneous implants of a poorly water-soluble active pharmaceutical ingredient (API) for potential long-acting therapeutic delivery. |
| **Methods:** In this work the APIs were referred to as API1 and API2. Solid drug nanoparticles (SDNs) were synthesised using the emulsion-templated freeze-drying method (ETFD); oil-in-water emulsions with a 1:4 DCM:water phase ratio were used with stabilising excipients in the aqueous phase and API in the organic phase. This was sonicated to form an emulsion before being frozen and all solvents were removed by lyophilisation to give 70 wt% loaded SDNs. The resulting porous monoliths were used to fabricate solid, cylindrical implants using vacuum compression moulding (VCM). This technique used a vacuum to apply pressure through a piston to a powdered sample in a PTFE tube, whilst being heated, to form a solid, cylindrical geometry. Release of API from these samples was then quantified using a Rapid Equilibrium Dialysis (RED) assay over 24 hours and analysed via HPLC. |
| **Results:** Dynamic light scattering (DLS) was used to determine the hydrodynamic diameter of the nanoparticles produced, with API 1 giving sizes between 700 – 850 nm and API2 between 100-250 nm. HPLC analysis of the RED assay release showed a steady release of API was observed over the course of the experiment, with a cumulative release of 93.0% API after 24 hours. These 70 wt% API loaded solid injectables, stabilised by a lone excipient of PVA (MW 9000-10,000), underwent pharmacokinetic analysis (PK) in rodents via subcutaneous injection. The results of this study showed a difference in API, with API 2 having peaked in concentration after only a few hours and then rapidly declining, whereas API 1 had sustained release over 91 days, until the experiment ended. |
| **Conclusions:** This study showed that API1 can be administered at a high concentration as a long-acting solid implantable to give a sustained release of API over several months. This proof of concept demonstrated that VCM can be used to produce solid injectable of poorly soluble drug compounds for long-acting drug delivery, giving hope for this methodology to be used with other APIs to offer sustained release in a clinical setting. |