|  |
| --- |
| **Development of Long-acting Injectable Solid Drug Nanoparticle Formulations of Investigational Antiretroviral Therapeutics** |
| James Hobson1, Catherine Unsworth1, Jonathan Massam1, Abdenour Djemai2, Trevor Riley3, Mark Johnson4, Andrew Owen1, and Steve Rannard1 |
| 1Centre of Excellence for Long-acting Therapeutics, Department of Chemistry, University of Liverpool; 2ViiV Healthcare, Brentford, UK; 3GSK, Stevenage, UK, 4 ViiV Healthcare, North Carolina, USA |
| **Background:** An estimated 38 million people globally are living with HIV, however advances in treatments mean that provided a patient has access to therapy, they can live a normal life. Further advances in treatment are still required, particularly with a view to improving patient adherence and offering new therapeutics that are not impacted by HIV resistance profiles. This study aimed to develop long-acting injectable (LAI) formulations for a new class of investigational active pharmaceutical ingredient (API) to treat HIV. |
| **Methods:** High throughput emulsion templated freeze drying (ETFD) screening was conducted using combinations of excipients that are listed on the FDA’s CDER list of inactive ingredients. In brief the ETFD screen involved taking the APIs dissolved in DCM and adding excipients dissolved in water, with the resultant two-phase mixture undergoing 15 seconds of sonication to form the emulsion. This emulsion was immediately frozen in liquid nitrogen and freeze dried for 48 hours to produce a porous dry powder containing stabilised API/excipient particles, with particle size determined by dynamic light scattering (DLS).Candidates identified from the ETFD screening were transferred to a non-chlorinated solvent precipitation method, using API dissolved in an 80:20 ratio of butanone and ethanol. The excipients remained dissolved in water and precipitation by addition of API to excipients under constant stirring. This methodology allowed for precipitated feedstocks to be spray dried using a Buchi B-290 to produce powders containing stable API/stabiliser particles. Formulations were assessed for powder stability, size distribution, and the maximum concentration achievable that could be administered via injection. |
| **Results:** Screening conducted at API loadings of 50 and 70 wt% with respect to total dry powder mass, yielded a total of 1350 combinations. Following assessment of physical characteristics, 109 of these were taken forward for lead optimisation, with 2 formulations selected for final scale up, full characterisation and production.Particle formation was confirmed via DLS analysis, amorphous characteristics were observed for API1 and semi crystalline characteristics for API2, as determined by pXRD and SEM analysis. The maximum syringable dosage was 300 mg/mL and 500 mg/mL respectively for each of the powders, via a 25g needle, suggesting suitability for LAI administration. Formulations remained stable as stored powders for 3 months under ambient and accelerated conditions. Chemical stability was determined by HPLC analysis, whilst particle stability and dispersibility confirmed by DLS and visual inspection. |
| **Conclusions:** A rapid, high throughput, formulation development process was designed and applied to formulation efforts for 2 investigational APIs. The lead candidate formulations showed good particle stability, reproducibility, and were amenable to laboratory production processes up to the multiple gram scale. The ability to form highly concentrated liquid depots of these formulations now warrants further pre-clinical *in vitro* and *in vivo* investigations to determine suitability as LAI administered therapeutics. |