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| **Application of solid drug nanoparticles of niclosamide to inhalation delivery through vibrating mesh nebulisation** |
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| **Background:** Niclosamide (NCL) is a cheap, broad-spectrum anthelmintic drug with reported activity against certain viral and bacterial agents, and bronchodilation properties. NCL is practically insoluble in water, resulting in very low bioavailability. As a result, the current oral formulation is unsuited to provision of the high systemic drug concentrations required for therapeutic activity, a hurdle which could be overcome through parenteral administration. Solid drug nanoparticle (SDN) generation techniques offer the opportunity to create excipient stabilised NCL nanoparticles, which can be redispersed in a range of aqueous media and administered through parenteral routes. |
| **Methods:** We have demonstrated scalable formation of NCL SDNs through nanoprecipitation in the presence of biocompatible excipients to produce a semi-crystalline material. NCL dissolved in a water-miscible solvent system is added rapidly to an aqueous phase, leading to supersaturation and nucleation. Stabilising excipients limit growth of NCL particles and a sonication phase breaks down any aggregates. Suspensions are immediately spray dried to remove solvents and produce a dispersible powder.  Aqueous dispersions of NCL were passed through a vibrating mesh nebuliser and pre- and post-nebulisation size characterisation and NCL concentration were determined by dynamic light scattering and gradient RP-HPLC. Cascade impaction of dispersions and HPLC analysis of collected droplet fractions were carried out on dispersions at 5 and 10 mg/mL NCL to assess droplet size and predict final location of deposition of droplets within the respiratory system. |
| **Results:** SDN powder optimised for inhalable delivery consisted of particles with hydrodynamic diameter (Dz) in the range of 700-800 nm, polydispersity index (PDI) in the range of 0.29-0.36, and NCL loading of 50 wt%. Reduction in Dz and PDI was seen post nebulisation at each dispersion concentration, HPLC quantification of NCL pre and post nebulisation suggested attrition of particles during nebulisation, rather than filtration.  Up to 70.4% of droplets were measured within the therapeutically relevant fine particle fraction range of 1-5 μm. Mass median aerodynamic diameters (MMAD) of 4.00 and 3.62 μm and geometric standard deviations (GSD) of 1.81 and 1.84 for the 5 and 10 mg/mL dispersions respectively suggest that these nebulised dispersions have small, low dispersity droplet fractions that are particularly suitable for targeted deposition in the middle respiratory region. |
| **Conclusions:** SDNs of NCL can be created with physical properties suitable for efficient nebulisation. The results of *in-vitro* studies suggest that aerosolised droplets of NCL SDN suspensions are suitably sized for site-targeted therapy in the lungs. Nebulisation of NCL suspensions offers a potentially effective and easily administrable option for the treatment of respiratory indications. |