PREPARATION, STABILISATION, ISOLATION AND TABLETING OF VALSARTAN NANOPARTICLES USING A SEMI-CONTINUOUS CARRIER PARTICLE MEDIATED PROCESS

Ajay Kumar[1], Kiran A. Ramisetty[1], Simone Bordignon[1], Benjamin K. Hodnett[1], Peter Davern[1] and Sarah P. Hudson[1]

[1] SSPC the Science Foundation Ireland Research Centre for Pharmaceuticals, Department of Chemical Sciences, and Bernal Institute, University of Limerick, Limerick V94 T9PX, Ireland

Background: Ninety percent of new drug entities and forty percent of approved drugs on the market have poor aqueous solubility which leads to unfavourable bioavailability. It is commonly accepted by the pharmaceutical industry and in academic literature that drug nanoparticles enhance the delivery and bioavailability of drugs with poor aqueous solubility when administered orally. Among the different techniques to form drug nanoparticles, liquid antisolvent precipitation is fast, easy and cost-efficient. However, it is challenging to scale-up in batch mode due to variations in local supersaturation resulting in wide particle size distributions within larger batch processing volumes. Another major challenge is the subsequent isolation of the nanoparticles to the solid state due to issues with particle growth and agglomeration. This work investigated the technical feasibility of preparing, stabilizing and isolating poorly water-soluble drug nanoparticles into nanocomposite powders and tablets with enhanced dissolution profiles, using a novel carrier particle technology.

Methods: A novel semi-continuous process was developed for the carrier particle mediated production, stabilization and isolation of valsartan (Val) nanoparticles into a solid form using montmorillonite clay (MMT) as the carrier particles. Tablets of nanocomposite powders at a range of drug loadings with just 10 % w/w disintegrant were formed. Particle sizing and zeta potential measurements were conducted as well as dissolution studies of powdered and tabletted nanocomposites. Small modifications to the surface of MMT using protamine, a cationic polymer, were made to facilitate high drug loadings.

Results: The semi-continuous process operated robustly for the entire duration of the experiment (~16 min) and steady-state conditions were reached after ~5 min. Nanoparticles of valsartan (51 ± 1 nm) were successfully prepared, stabilized and isolated with the help of montmorillonite (MMT) or protamine functionalized montmorillonite (PA-MMT) up to 33.3 % w/w drug loading into the dried form by this semi-continuous route. The dissolution profile of the isolated valsartan nanocomposite solids and their tablet formulations were similar to those produced via the corresponding laboratory scale batch mode process, indicating that product quality is retained during semi-continuous processing of the nanoparticles, which can be easily compressed into tablets without compromising the dissolution behaviour.

Conclusions: The developed semi-continuous process in this study offers a rapid and robust template for preparing stable drug nanosuspensions, which can then be readily isolated via adsorption (at different drug loadings) onto inert carrier particles. The resulting drug-carrier particle nanocomposite solids are suitable for tableting, affording fast-dissolving tablets for oral dosage forms.