FORMULATION OF DUAL COMPONENT SOLID DRUG NANOPARTICLES FOR IMPROVED ORAL BIOAVAILABILITY OF DARUNAVIR AND RITONAVIR

Alison C. Savage,[1] Samantha J. Ashcroft,[1] Helen Box,[2] Joanne Sharp,[2] Darren Moss,[2] Megan Neary,[2] Andrew Owen[2] and Steve P. Rannard[1]

1. *Department of Chemistry, University of Liverpool, Crown Street, Liverpool, L69 7ZD*
2. *Department of Molecular and Clinical Pharmacology, Materials Innovation Factory, University of Liverpool, Liverpool, L7 3NY*

Contact Email: alison.savage@liverpool.ac.uk

Many active pharmaceutical ingredients (API) exhibit poor aqueous solubility, which can often impact on the bioavailability of the drug when taken as a therapy. Recently, a strategy for formulating antiretroviral drugs into solid drug nanoparticles (SDNs) has been presented, with the resulting products exhibiting enhanced oral pharmacokinetics (PK). Preparation of these nanoparticles relies on an emulsion-templated freeze-drying method to screen different polymers and surfactants, with the drug dissolved in an organic phase and water soluble polymers and surfactants present in the aqueous phase. Once ideal excipients are identified and studied for reproducibility, stability and pharmacological behaviour, the method can be translated to spray-drying for scale-up and manufacture. Antiretroviral drugs are often taken in combinations as part of a HIV drug regimen which act on multiple viral targets. This is known as highly active antiretroviral therapy (HAART) and often involves antiretroviral drugs being administered with ritonavir, known to boost the half-life of certain antiretrovirals.

We have adopted the solid drug nanoparticle strategy with the anti-retroviral drugs Darunavir (DRV) and Ritonavir (RTV) to prepare dual component SDNs to combine two APIs into one nanoparticle-containing powder feedstock. *In vitro* pharmacological testing isolated the best performing formulation by determining the apparent permeability of the SDNs across Caco-2 and triple culture monolayers, whilst *in vivo* studies established its steady state pharmacokinetic profile. Steady-state multiple-dosing studies determined, using an initial loading dose followed by a 50 % lower maintenance dose, that there is potential for considerable dose reduction without compromising PK exposure. This data provides preclinical demonstration of the world's first DRV/RTV fixed-dose-combination formulation with a potential for dose reduction of both DRV and RTV whilst maintaining drug concentrations in the therapeutic window. The scale-up of the best SDN candidate by spray-drying has provided the manufacturing scale necessary to potentially pursue first in human clinical evaluation.

Back to Programme