DEVELOPMENT OF A SUSTAINED-RELEASE TABLET FORMULATION OF NOVEL ANTIHYPERTENSIVE DRUG MT-1207

Napoleon-Nikolaos Vrettos[1], Peng Wang[2,3], Yan Zhou[3], Clive Roberts[1], Jinyi Xu[2], Hong Yao[2], Zheying Zhu[1]

[1] School of Pharmacy, University of Nottingham, Nottingham, United Kingdom

[2] Institute of Pharmaceutical Sciences, China Pharmaceutical University, Nanjing, China

[3] Shenyang Haiwang Biotechnology Co. Ltd., Shenyang, China

Background: Hypertension is one of the most common chronic cardiovascular disorders. Controlled-release formulations can be used to maintain drug concentration within therapeutic levels throughout the treatment and increase patient compliance. The purpose of the present study was to develop a once-a-day tablet formulation for the novel antihypertensive agent MT-1207.

Methods: A tablet manufacturing method was developed and optimised, including wet granulation of the powder mixture containing the drug and the excipients, prior to compression. The matrix tablets produced were characterised for hardness, friability, uniformity of weight and *in vitro* release of MT-1207. Furthermore, Fourier Transform InfraRed (FTIR), differential scanning calorimetry (DSC) and X ray powder diffraction (XRPD) analyses were carried out as part of the physical characterisation of the tablets. Additionally, *in vitro* drug release studies were carried out in a dissolution medium of 0.1 M phosphate pH 6.8 with 0.2% w/v sodium dodecyl sulfate (SDS) using USP II paddle apparatus. Finally, *in vivo* animal studies were performed in Beagle dogs for the optimised sustained-release and immediate-release tablets.

Results: The tablets containing HPMC K4M could not retard the release of MT-1207. When this polymer was substituted with HPMC K15M which has higher molecular weight and viscosity than HPMC K4M a sustained release of MT-1207 from the tablets was achieved. Formulation F4 containing 31% w/w HPMC K15M gave a 24-hour release of MT-1207 with an almost constant release rate up to 20 hours. *In vivo* studies were then carried out in Beagle dogs for F4 and for the MT-1207 immediate-release tablets. The results showed that a sustained release of MT-1207 from F4 was achieved since the drug $t_{1/2}$ value was 2.5 times higher than that obtained after oral administration of the IR tablets. Moreover, the $AUC_{0-\infty}$ values of both sustained- and immediate-release tablets were identical at the same MT-1207 dose (30 mg) which showed that the same amount of drug was absorbed in each case.

Conclusions: A 24-hour sustained release of MT-1207 from the 30 mg optimised tablet formulation was achieved *in vitro*. However, *in vivo* studies in Beagle dogs showed that the plasma concentration of MT-1207 was not sustained over 24 hours and potentially the drug levels were below the therapeutic window at the 24-hour timepoint. Therefore, further optimisation of the formulation is probably needed, in alignment with pharmacological data that are expected from phase II clinical trials of the immediate-release tablets.