DEVELOPMENT OF A BIODEGRADABLE SUBCUTANEOUS IMPLANT FOR THE TREATMENT OF HYPOTHYROIDISM

Sarah Stewart [1], Juan Domínguez-Robles[1], Emilia Utomo [1], Camila Picco [1], Ryan Donnelly[1], Eneko Larrañeta[1]

[1] School of Pharmacy, Queen's University Belfast, BT9 7BL, UK

Background: Deficiency of thyroid hormones (hypothyroidism) is thought to effect more than 1.3 million people in the UK. Thyroid hormones control many physiological processes and deficiency causes symptoms such as chronic fatigue, weight gain and cold intolerance. Treatment with oral levothyroxine (LEVO) is the current standard. However, the effectiveness of oral administration is highly dependent on the co-administration of food and other drugs. As such, LEVO is recommended to be taken at least 30 minutes before food and other medication. These additional directions and the chronic nature of this condition mean that there are concerns with patient compliance. This work aimed to develop a subcutaneous implant for prolonged delivery of LEVO to treat hypothyroidism. This could overcome challenges with patient compliance and co-administration and could improve treatment of this condition. Stability of LEVO sodium in solution is a known challenge and as such a suitable biorelevant medium for extended *in vitro* release studies and an appropriate quantification method needed to be developed.

Methods: Implants were produced by solvent casting mixtures of poly(caprolactone) (PCL), poly(ethylene glycol) (PEG) and LEVO sodium. Formulations were prepared from mixtures of PCL of differing molecular weight, PEG and different LEVO sodium loadings (20% or 40% w/w). Implants were characterised using DSC, FTIR and SEM.

LEVO sodium stability in a range of release media was investigated and the most suitable was chosen to conduct release studies in. *In vitro* release studies were performed in 0.1% bovine serum albumin (BSA) and at predetermined time points the entire release medium was replaced. LEVO sodium release was analysed using HPLC (Zorbax Eclipse plus C_{18} column (4.6 x 250 mm) with guard column of matching chemistry, a mobile phase of acetonitrile: 0.1% trifluoracetic acid (50:50% v/v), a flow rate of 0.6 mL/min, an injection volume of 50 µL and a detection wavelength of 225 nm).

Results: Rod shaped implants of 2.5 x 40 mm were successfully produced by solution casting into silicone moulds. Implants prepared containing PEG showed an immediate discoloration and stability studies indicated an instability of LEVO sodium in PEG. FTIR, SEM and DSC results suggest that LEVO sodium in insoluble in the solvent used and is dispersed throughout, but not interacting with, the polymer matrix.

Quantification of LEVO sodium was achieved using RP-HPLC coupled with UV detection. This method was linear in the range 0.012 – 25 µg/mL and had a limit of detection and quantification of 0.03 and 0.09 µg/mL, respectively. LEVO sodium was found to be stable in 0.1% BSA for at least 14 days and as such this was chosen as the release medium for *in vitro* release studies. Release rates ranging from 42.01 ± 3.98 – 109.07 ± 6.17 µg/day and 101.41 ± 15.64 – 106.95 ± 16.77 µg/day were achieved for formulations containing 20% and 40% drug loading, respectively.

Conclusions: The implants produced in this work showed promising *in vitro* release rates for the delivery of LEVO sodium for the treatment of hypothyroidism. Future work will aim to optimise the implant formulation and investigate *in vivo* release rates.