DEVELOPMENT OF ANTIBIOTIC HYDROGEL-FORMING MICRONEEDLE ARRAY PATCHES FOR IMPROVED TUBERCULOSIS TREATMENT

Qonita Kurnia Anjani [1], Eneko Larrañeta[1], Ryan F. Donnelly[1]

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

Background: Tuberculosis (TB) is one of the leading causes of death worldwide. Suggests one-quarter of the world's population has been infected by *Mycobacterium tuberculosis*. The current available treatment for TB consists of rifampicin (RIF), isoniazid (INH), pyrazinamide (PYR) and ethambutol (ETH). However, this regimen has been reported causing hepatotoxicity as the most frequent adverse effect triggered by daily oral administration for at least 6 months. Transdermal drug delivery using microneedle array patches (MAP) technology is considered as a promising alternative in delivering TB drug regimen. This route offers a non-splanchnic circulation, thus, pre-systemic metabolism in the liver is avoided. A drug reservoir combined with hydrogel-forming MAP used in this present work which aims to deliver a high dose of TB drugs. Hydrogel-forming MAP are formed through a cross-linking of two or more polymers. This system consists of micron-sized needles that can be used to penetrate the deeper layer of skin, thus, allowing the drug permeated and reached the microcirculation for the systemic absorption.

Methods: The hydrogel-forming MAP (11 × 11 needles and 600 μm in height) were prepared from an aqueous blend containing Gantrez® S-97 (co-polymer of methylvinylether and maleic acid), polyethylene glycol (PEG) 10,000 and sodium bicarbonate. An individual reservoir containing each drug was prepared using a directly compression method. Crospovidone was used as a disintegrant in the direct compressed tablet (DCT) formulations of RIF, INH and PYR. In the specific case of ETH, based on the preliminary result, the DCTs were prepared by compressing only the pure drug without any disintegrant. A central composite design (Design Expert Software version 12, State-ease, Minneapolis, USA) was applied to optimise the reservoir formulations by using two parameters: dissolution time and tablet hardness. The optimised formulations were then investigated in *in vitro* permeation studies to quantify the amount of drugs that permeated across the dermatomed neonatal procine skin through the hydrogel-forming MAP over 24 hours.

Results: All optimised formulations of DCTs exhibited homogeneous and robust properties. The dissolution time and hardness values of the optimised formulations were in the range of 10-12 sec and 33-58 N, respectively. Following the *in vitro* permeation studies, TB drugs were able to permeate across the dermatomed neonatal porcine skin from the DCT reservoirs combined with hydrogel-forming MAP. The result showed that a 0.5 cm^2 MAP delivered 0.69 mg, 30.96 mg, 25.71 mg and 46.99 mg in 24 hours for RIF, INH, PYR and ETH, respectively. The permeation profiles suggest a promising transdermal delivery of TB drugs.

Conclusions: In this present work, the reservoir formulations of TB drug regimen combined with hydrogel-forming MN arrays were successfully developed. Based on the *in vitro* permeation studies, the developed MAP system was able to deliver the TB drugs across the dermatomed neonatal porcine skin. Therefore, this approach could potentially contribute to the TB treatment improvement.