Dissolving microneedle-mediated long-acting drug delivery of rotigotine formulations

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Background: Parkinson's disease (PD) is one of the most common neurodegenerative central nervous system (CNS) diseases currently affects approximately 10 million of people all over the world. It is characterised by the loss of dopaminergic neurons. Rotigotine (RTG) is a typical non-ergoline dopamine agonist with a preference for D3 receptors and the first approved transdermal medication for the treatment of PD. It has a half-life of 5-7 hours and 37% bioavailability. LogP and pKa values are 4.3 and 10.03, respectively. RTG transdermal patch (Neupro®) is a once-daily administered treatment with the dose ranging from 2-18 mg/day). Thus, potential improvement in frequent administration and relatively low bioavailability are two focuses in future RTG researches. Microneedle (MN) arrays are painless transdermal drug delivery systems, which enables the direct penetration of *Stratum Corneum (SC).* The aim of this project is to develop dissolving MNs loaded with RTG formulations, which intends to form an intradermal depot under the skin and further be released into the systemic circulation.

Methods: A quantification method for RTG was first developed. A 'top-down' beads milling method was applied to prepare the RTG NS. A 7 ml glass vial was utilised as the milling chamber. Two types of magnetic stirring bars, namely 25 x 8 mm and 12 x 6 mm bars were compared in terms of resulted polydispersity index (PDI) and particle size. PVA (9-10K Daltons), PVP (K-29/32), Poloxamer 188 and Tween 80® were screened based on their influences on PDI and particle size. Three types of beads with the diameter of namely 0.1 mm, 0.4 mm and 1.1 mm were compared as well. The milling chamber was placed on a magnetic stirrer for 24 h with the speed of 1200 rpm. Prior to lyophilisation process, PVP (K-29/32) was added to the NS as the cryoprotectant in a 1:1 weight ratio with stabiliser content. Dissolving MNs were manufactured by a two-layer casting technique. The mould contained 16 x 16 needles with the height of 850 μm. An excess of drug-containing layer, which composed of 95 mg lyophilised RTG-NS powder mixed with 200 μL deionised water with the aid of SpeedMixer at 3000 rpm for 5 mins, was spread over the moulds center and pressure chamber was applied for 2 mins to push the formulation towards the needle tips. After the removal of the excessive first layer formulation, another 30 mins of 5 bar pressure further ensured the accumulated drug content in the needle tips. The second layer was cast by addition of 850 μL 30% w/w PVP (K-90) and 1.5% w/w glycerol mixture on the top, followed by centrifuge at 3500 rpm for 2 mins. The MN was then left to dry in the room temperature for 48 h and characterised by the light microscope.

Results: A specific and sensitive HPLC-UV quantification method for RTG was successfully developed and validated according to International Council of Harmonisation (ICH) Q2(R1). Limit of quantification (LoQ) was 2 μg/ml and limit of detection (LoD) was 0.67 μg/ml. The RTG-NS was manufactured by 5 ml 1% w/w PVA (9-10K Daltons) solution as the stabiliser, 200 mg RTG and 2 ml 0.1 mm beads. The NS particle size was 307.17 ± 1.25 nm with the polydispersity index (PDI) of 0.174 ± 0.02 (n=3). The manufactured RTG-NS MNs were well-formed in terms of morphology and possessed good mechanical strength for insertion.

Conclusions: A specific and sensitive quantification method was successfully developed and validate. The manufacture method for RTG NS was developed and successfully loaded into dissolving MN by a two-layer casting technique. In the next stage, optimised RTG-NS and RTG powder will be loaded into MN for comparison in terms of drug loading efficiency, MN characteristics and *in-vitro*, *in-vivo* release profiles.