

Dissolving microneedle-mediated long-acting delivery of rotigotine formulations

Yaocun Li¹, Lalitkumar Vora¹, Alejandro J. Paredes¹, Ismaiel Tekko¹, Ryan F. Donnelly¹
¹School of Pharmacy, Queen's University Belfast, BT9 7BL, United Kingdom

Introduction

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(1). Rotigotine (RTG) is a typical non-ergoline dopamine agonist with the 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(2). 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)(3). 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

- Development of RTG nanosuspension (NS) fabrication method
A 7 ml glass vial was applied as the milling chamber. The magnetic stirring bars was 25 x 8 mm in size. PVA (9-10K Daltons) was selected as the stabiliser based on the resulted polydispersity (PDI) and mean particle size. Ceramic beads with the diameter of 0.1 mm was utilised for the milling process inside the glass vial. The milling chamber was placed on a magnetic stirrer for 24 h with the speed of 1200 rpm as shown in Figure 1.



Figure 1 Schematic presentation of NS manufacture

- Fabrication of dissolving MN loaded with RTG formulations
Dissolving MNs were manufactured by a two-layer casting technique. The mould for manufacture contained 16 x 16 needles with the height of 850 μm . The drug-containing layer was composed of 95 mg lyophilised RTG-NS powder and 200 μL deionised water. The second layer was prepared by 30% w/w PVP (K-90) and 1.5% w/w glycerol mixture. The schematic presentation was shown in Figure 3.

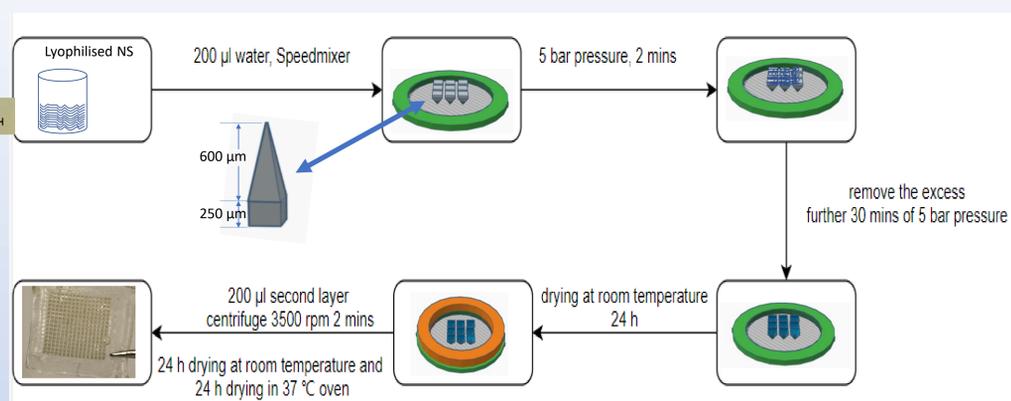


Figure 2 Diagrammatic presentation of two-layer MN casting process

Results

The RTG NS was successfully developed on the nano-scale. The dynamic light scattering (DLS) instrument was applied for nanoparticle sizing. After 24 h of milling, the resulted NS mean particle size was 307.17 ± 1.25 nm with the PDI value of 0.174 ± 0.02 (n=3). The representative DLS graph was illustrated in Figure 3.

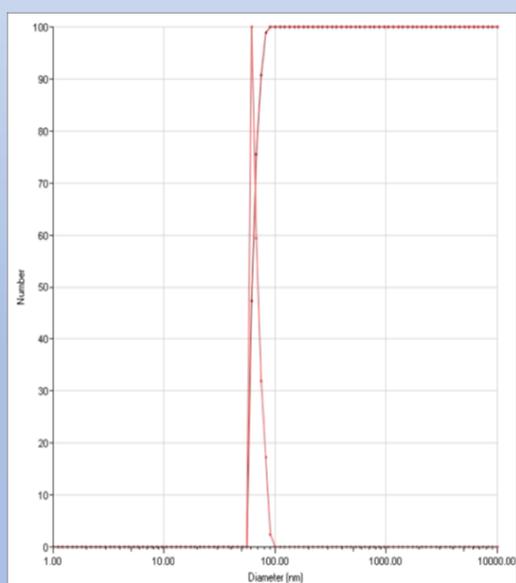


Figure 3 Representative DLS graph of RTG NS

The two-layer RTG NS loaded dissolving MN was fabricated. The overall and specific morphology were illustrated in Figure 4. As it suggested in the microscopy images, the RTG NS loaded MN was homogenised and exhibited the separation between the drug-containing layer and drug-free layer. The average needle height was 830 ± 50 μm . Further investigation about mechanical strength and insertion properties should be carried out.

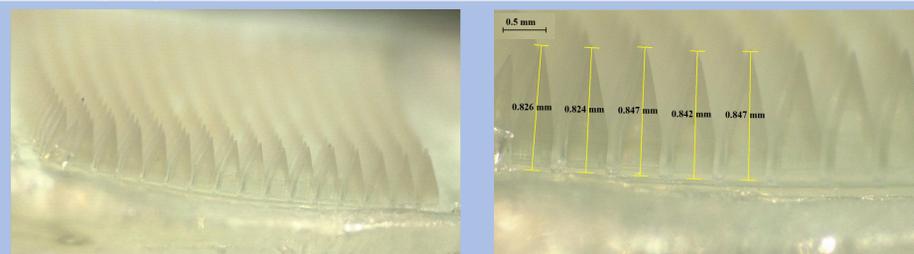


Figure 4 Overall and specific microscopy images of RTG NS loaded MNs

Conclusions

The 'top-down' manufacture method for RTG NS was developed and the resulted formulations were successfully loaded into dissolving MN by a two-layer casting technique. In the next stage, optimised RTG-NS and bulk RTG powder will be loaded into MN for comparison in terms of drug loading efficiency, MN characteristics and in-vitro, in-vivo release profiles.

References

- Davie CA. A review of Parkinson's disease. British Medical Bulletin. 2008;86(1):109-127.
- Reynolds NA, Wellington K, Easthope SE. Rotigotine. CNS Drugs. 2005;19(11):973-981.
- Prausnitz MR. Microneedles for transdermal drug delivery. Advanced drug delivery reviews. 2004;56(5):581-587.