MANUFACTURE OF DISSOLVING MICRONEEDLE LOADED WITH NANOSUSPENSION: POTENTIAL FOR PROLONGED LOCAL ANTI-INFLAMMATORY EFFECTS

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most commonly used drugs at present. Approximately 30 million people consume NSAIDs every day around the world. NSAIDs block the effect of cyclo-oxygenase (COX) enzymes to ease the pain and inflammation. Diclofenac (2-(2,6-dichloranilino) phenylacetic acid) belongs to NSAIDs and it is prominently used in osteoarthritis, ankylosing spondylitis, rheumatoid arthritis treatments and some post-operative pain management. This project involves loading diclofenac nanosuspensions into dissolving microneedles (MNs) to achieve anti-inflammatory effects.

Methods: Diclofenac nanosuspension (NS) was manufactured by beads milling methods. A 7 mL glass vial contains 5 mL polymer blends composed of 9-10 kDa poly (vinyl alcohol) (PVA) and K-29/32 poly (vinyl pyrrolidone) (PVP). 200 mg of diclofenac drug powder and 2 mL of 0.1 mm beads were added into the glass vial. Four 12x6 mm stir bars in the vessel rotated at 1200 rpm. The particle size of diclofenac was measured at different time points. After 20 hours, the milling process was stopped and the final particle size of NS was measured by DLS. Following the milling process, water was removed from the NS by freeze-drying the formulation. Dissolving MNs were cast through a two-step process. The first layer formulations of MNs were freeze-dried diclofenac NS mixed with water. The second layer was a drug-free polymer baseplate which could be formed by RS PRO PLA or 40% K90 PVP gel. Moulds used to make MNs were round silicon moulds contained 600 pyramidal needles with a height of 750 μm, 14x14 moulds with conical needles (500 μm), 19x19 moulds with pyramidal needles (500 μm) and 16x16 silicon moulds with pyramidal needles (850 μm). Formed MNs were left at room temperature to dry. Dried MNs were dissolved in 5 mL water and sonicated until uniform solutions were obtained. Then 100 μL solutions was diluted to 1 mL by ACN and filtered into HPLC vials by 0.2 μm PTFE membranes. The drug contents of MNs were quantified by HPLC. At the same time, 1 mL dissolved MN solutions were diluted to 3 mL by water in cuvettes. The particle size of diclofenac was measured by DLS. In the insertion study, MNs were placed into 37 ℃ oven for more than 30 mins and then were applied on the full-thickness porcine skin for 30 seconds. Insertion performances were observed under OCT.

Results: The diclofenac drug powder had a particle size of 114 microns. During the milling process, after 3 hours, diclofenac NS had a particle size of 281.97±21.99 nm (n=10) and after 6 hours had a particle size of 241.53±11.87 nm (n=10). After 20 hours, the particle size of diclofenac NS decreased to 192.85±12.86 nm. Particle size was retained during freeze-drying. All four types of MNs were well-formed and had good insertion performances. The MNs with PLA baseplate dissolved quicker. Also the particle sizes of diclofenac in dissolved MNs with PLA baseplate retained as the original sizes. However MNs with PVP baseplate were difficult to dissolve and particle sizes increased compared with original sizes. The drug content of round MNs (750μm) was 2.3mg (n=5) and it could increase to 3.1mg (n=3). For 14x14 MNs (500μm), the drug content was 1.3mg (n=6). 19x19 MNs (500μm) had 1.2mg (n=6) drug loading and 16x16 MNs (850μm) had 2.3mg (n=6) drug loading.

Conclusions: NS of diclofenac were successfully fabricated *via* beads milling method and significantly decreased the particle size of diclofenac. Four types of dissolving MNs with two different baseplates were well-formed and showed good insertion properties. The MN contained 600 pyramidal needles (750 μm) had the highest drug loading. Further studies are now needed to assess the *in vitro* release and delivery of the drug from these MNs.