DEPOT FORMING MICRONEEDLES FOR THE LONG ACTING DELIVERY OF A MODEL DRUG; ATORVASTATIN

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Background: Sustained release dosage forms are designed to achieve an extended therapeutic effect by continuously releasing medication over a prolonged period after the administration of a single dose. This has many advantages over the conventional drug delivery methods, such as reducing the undesired fluctuations of drug levels in plasma, reducing the doses frequency and thus improve patients' compliance to their treatment regimens. However, to achieve sustained release over a week or more, injections must be used. This possesses many disadvantages including the difficulty to terminate the treatment in case of drug toxicity. Moreover, the sterility and pyrogen-free requirements for a parenteral product can potentially increase the manufacturing costs of these products. Therefore, in this project, microarray patches (MAPs) are used to deposit a model hydrophobic drug; atorvastatin (ATR), intradermally, to provide a sustained release from a depot in the skin over a prolonged period of time.

Methods: MAPs were fabricated from aqueous blends containing 20% w/w Gantrez® S-97, a copolymer of methyl vinyl ether and maleic acid (PMVE/MA) with 7.5% w/w poly(ethylene glycol) 10,000 and 3% w/w sodium carbonate (Na_2CO_3). They were centrifuged casted into moulds consisting of 361 microneedles (19x19) on a 0.5 cm^2 area, dried at room temperature and crosslinked in an 80°C oven. The drug reservoirs were prepared using the cosolvent method, where a high molecular weight polymer (PEG 6,000 25% w/w) was added to a mixture containing a low molecular weight polymer (PEG 200 75% w/w) and a drug (ATR).The mixture was then casted into square tablets moulds, each had an area of 1cm^2, a mass of 0.25g and contained 15 mg ATR. To test the drug release *in vitro,* Franz cells were used. Dermatomed neonatal porcine skin (~350 µm thick) was attached to glass donor compartment using cyanoacrylate glue. MAPs were the inserted using manual pressure. The drug reservoir was placed on top of the MAP, then a metal weight of 5 g was put on the top to hold the set still. The receiver compartment contained 12 mL of the release media. The donor compartment was placed on top of the receiver compartment and they were clamped. Samples were taken at predefined time points and were replaced by fresh media. After 24 hours, the cells were dissembled, and the drug was extracted from skin, MAPs and remaining drug reservoirs samples and analysed using HPLC.

Results: Samples of the Franz cells were taken at predetermined time points of 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 24 hours and analysed using a validated method on HPLC to calculate amount of ATR in each sample. The mean amount of ATR delivered after 24 hours was 3.73 ± 1.65 mg per patch, which stands for 25.01% of ATR amount in the reservoir (n=3). The mean amount of drug recovered from the MAPs was 2.01 ± 1.5, which accounts for 2.68% of the initial amount of drug loaded into the reservoir. Whereas 0.49 ± 0.05 mg was obtained from the skin samples, accounting for 0.66% of the total amount of drug. Furthermore, samples obtained from the remaining drug reservoirs contained 4.99 ± 2.2 mg ATR, and that accounts for 6.65% of the total amount of drug. To sum up, a total amount of 11.34 ± 0.14 mg ATR was recovered after analysing all Franz cells samples, which represents 75.61± 1.14% of the drug loaded into the reservoirs.

Conclusions: The formulation of ATR in PEG reservoirs, to be used in a combined MAPs system, proved both possible and effective in facilitating transdermal delivery of this hydrophobic compound. Further skin deposition studies are to follow to assess the amount of ATR that can be deposited in the skin for a sustained release from this depot.