Depot Forming Microneedles For The Long Acting Delivery Of A Model Drug; Atorvastatin

Yara A. Naser, Qonita K. Anjani, Eneko Larrañeta, Ryan F. Donnelly

Queen's University Belfast, School of Pharmacy, Belfast BT9 7BL, Northern Ireland, U.K.

For further details please contact: ynaser01@qub.ac.uk

Introduction:

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 [1,2]. 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 [3]. Moreover, the sterility and pyrogen-free requirements for a parenteral product can potentially increase the manufacturing costs of these products [4]. 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 as shown in Figure 1 below.

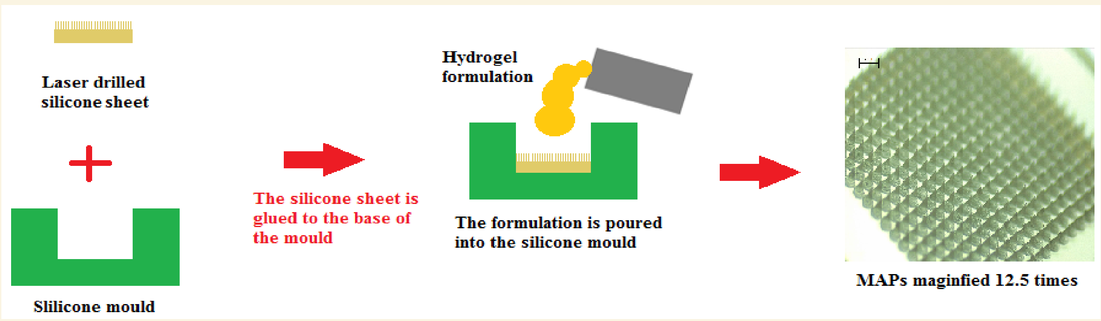

Figure 1: Schematic representation of the steps required to cast the hydrogel-forming MAPs.

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 0.25 g and contained 15 mg ATR.

To test the drug release *in vitro,* Franz cells were used (Figure 2). 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.

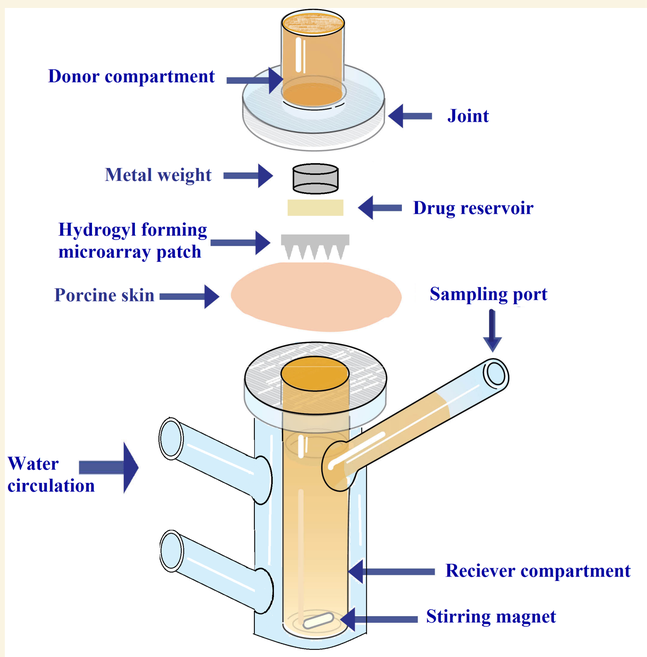

Figure 2: Schematic representation of Franz cells set up.

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 quantify amount of ATR in each sample. Figure 3 shows ATR amount and percentage delivered over 24 hours through Franz cells and extracted from MAPs, skin and the drug reservoirs.

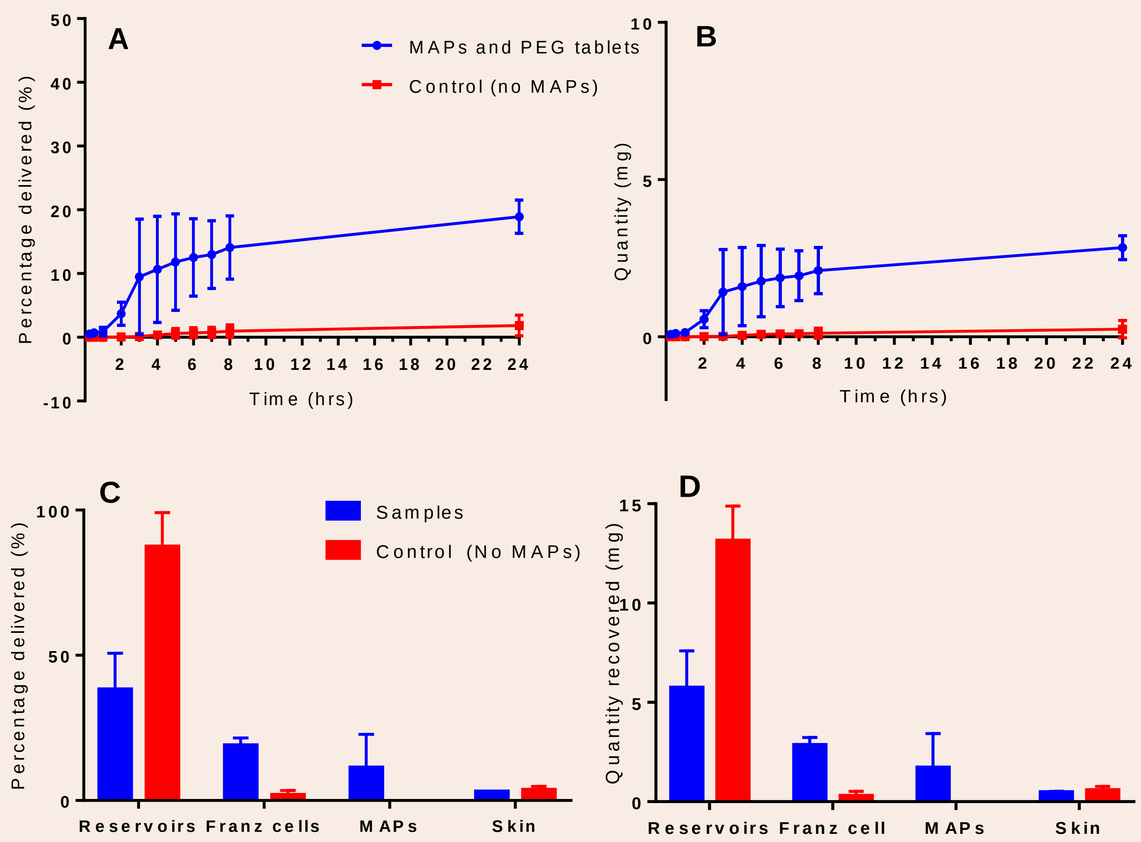

Figure 3: (A) Illustrates the percentage delivered into the donor compartment over 24 hours. (B) Represents the quantity delivered in mg over 24 hours. Mean ± SD, n=3. (C) Shows the percentage of drug extracted from reservoirs, MAPs and skin where (D) represents the quantity (mg). Mean + SD, n=3.

Figure 4 below shows MAPs and reservoir remaining after 24 hours in tablets-only (control) cells and in cells containing the MAPs with the drug reservoirs.

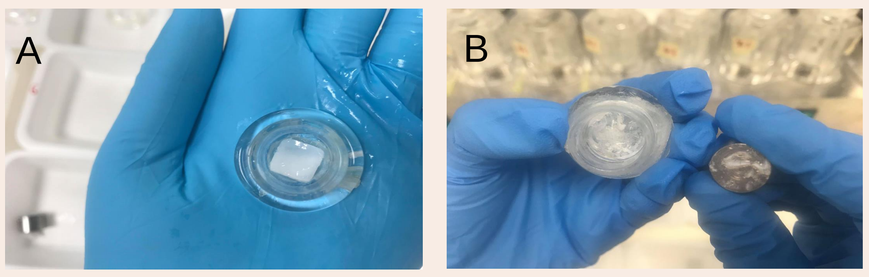

Figure 4: (A) Reservoir remaining after 24 hours in the control cells. (B) Reservoir remaining after 24 hours in cells containing MAPs.

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.

References:

1. Steve I. Shen, B.R.J., Xiaoling Li, Design of controlled-release drug delivery systems, in Standard handbook of biomedical engineering and design. 2004.
2. Vijayakumar, V. and K.G. Subramanian, Drug carriers, polymers as: synthesis, characterization, and in vitro evaluation, in Encyclopedia of Biomedical Polymers and Polymeric Biomaterials. 2016.
3. Nikita P. Karode, V.D.P., Himanshu K. Solanki, Girish K. Jani, Sustained release injectable formulations: its rationale, recent progress and advancement. World Journal of Pharmacy and Pharmaceutical Sciences, 2015.
4. Shi, Y. and L.C. Li, Current advances in sustained-release systems for parenteral drug delivery. Expert Opinion Drug Delivery, 2005.