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Intradermal Delivery of a Near-infrared Photosensitizer Using Dissolving Microneedle Arrays

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ABSTRACT

Nodular basal cell carcinoma is a deep skin lesion and one of the most common cancers. Conventional photodynamic therapy is limited to treatment of superficial skin lesions. The parenteral administration of near-IR preformed photosensitizers suffers from poor selectivity and may result in prolonged skin photosensitivity. Microneedles (MNs) can provide localized drug delivery to skin lesions. Intradermal delivery of the preformed near-IR photosensitizer; 5,10,15,20-tetrakis(2,6-difluoro-3-*N*-methylsulfamoylphenyl bacteriochlorin (Redaporfin™) using dissolving MN was successful *in vitro* and *in vivo*. MN demonstrated complete dissolution 30 min after skin application and showed sufficient mechanical strength to penetrate the skin to a depth of 450 μm. *In vitro* deposition studies illustrated that the drug was delivered and detected down to 5 mm in skin. *In vivo* biodistribution studies in athymic nude mice Crl:NU(NCr)-*Foxn1*^{nu} showed both fast initial release and localized drug delivery. The MN-treated mice showed a progressive decrease in the fluorescence intensity at the application site over the 7-day experiment period, with the highest and lowest fluorescence intensities measured being $9.2 \times 10^{10} \pm 2.5 \times 10^{10}$ and $3.8 \times 10^{9} \pm 1.6 \times 10^{9}$ p/s, respectively. By day 7, there was some migration of fluorescence away from the site of initial MN application. However, the majority of the body surfaces showed fluorescence levels that were comparable to those seen in the negative control group. This work suggests utility for polymeric MN arrays in minimally invasive intradermal delivery to enhance photodynamic therapy of deep skin lesions.

Introduction

Nonmelanoma skin cancer continues to be the most common type of cancer in the world, as estimated by the World Health Organization (2017). Photodynamic therapy (PDT) is a noninvasive procedure that has been widely used in treating nodular basal cell carcinoma, a major subtype of nonmelanoma skin cancer.[1] PDT involves the use of light of a specific wavelength and a photosensitiser in the presence of molecular oxygen to generate reactive oxygen species (ROS) that destroy targeted cells. PDT selectivity is attributed to photosensitizers' affinity for tumors, the very limited diffusion distance of the ROS generated and directionality of laser light.[2]

To treat deep skin cancers, such as nodular basal cell carcinoma effectively, it is essential to use light that is capable of penetration to the bottom of such lesions, which can often extend to depths of 5 mm. The near-IR (NIR) region of the electromagnetic spectrum, between 650 and 850 nm, offers maximal penetration of light, because it avoids endogenous chromophores and absorption by water.[3] Light in this region has a relatively lower scattering and absorption by tissue components. The parenteral administration of NIR preformed photosensitizers suffers from poor selectivity and may result in prolonged skin photosensitivity. Topical drug delivery directly to a skin lesion offers the potential to reduce side effects. Today, there is an increasing interest in microneedle (MN) technology in the field of topical drug delivery. MN, minimally invasive

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Table 1
Calibration Curve Properties for Redaporfin™ Quantification in Ethanol:DMSO (75:25%) and *LoD*) and *LoQ* for Redaporfin™

Solvent	Slope	*y*-Intercept	R^2	*LoD* (μg/mL)	*LoQ* (μg/mL)
Ethanol:DMSO (75:25)%	0.057	0.0005	1	0.011	0.034

LoD, limits of detection; LoQ, limits of quantification.

arrays of microscopic projections, has the potential to provide a localized drug delivery. MN allows numerous substances to be delivered into the skin that would otherwise be unable to penetrate the formidable *stratum corneum* barrier.[4]

Among the large number of photosensitizers that have been evaluated for their activity, only a limited number have proceeded into clinical trials.[5-7] Photosensitizers which have high molar absorptivity, low dark toxicity (i.e., toxicity in the absence of light), high phototoxicity, amphiphilicity, long shelf-life, and rapid clearance are desired.[7] Naturally occurring bacteriochlorins and their derivatives meet most of the requirements for an ideal PDT agent. Nevertheless, they suffer from photo and thermal instabilities.[7,8] As a result of extensive research to improve the properties of PDT photosensitizers,[8-23] a new synthetic bacteriochlorin which belongs to the class of halogenated sulfonamide bacteriochlorins photosensitizers (Redaporfin™, also named F2BMet and LUZ11) was developed.[7] Redaporfin™ proved to be safe and effective[24] and a competitive alternative to the existing PDT agents. Redaporfin™ demonstrated superior photostability, extended lifetimes in the excited triplet state, favorable biodistribution, and high ROS quantum yield in *in vivo* studies conducted by Arnaut et al.[7] and Saavedra et al.[25] Redaporfin™ is not an extremely lipophilic photosensitizer, examples of which typically possess low biocompatibility and precipitate in the aqueous media of the body. However, it is not especially hydrophilic either, since such compounds typically have reduced activity because they tend to accumulate in the tumor stroma.[22,26]

Although Redaporfin™ has many characteristics of an ideal photosensitizer, a well-designed drug delivery system should enhance drug availability in the target tissue, preferably after a minimum drug-to-light interval (DLI) for patient convenience. Tumor-to-muscle (T/M) ratio, which describes selectivity of retention of a photosensitizer in solid tumors, is generally increased for longer DLIs, However, this declines as a function of time because of photosensitizer clearance from the body. Prolonged skin photosensitivity after treatment, which is a major inconvenience for patients, should also be taken into consideration. Hence, high tumor-to-skin (T/S) ratios and fast clearance of the photosensitizer after treatment are both desirable.[25] Photosensitizer formulations have been the subject of much research to address drug availability at the site of action and skin photosensitivity issues to enhance PDT efficacy and improve patients' quality of life.[27-31]

This study aimed to explore the potential of dissolving MN arrays for the delivery of a model NIR-preformed photosensitiser; Redaporfin™, *in vitro* across full-thickness neonatal porcine skin, followed by *in vivo* biodistribution in athymic nude mice Crl:NU(NCr)-*Foxn1*^{nu}. For the first time, an NIR preformed photosensitizer was successfully delivered using a polymeric dissolving MN system. We showed that a suitable formulation for such a drug has a profound impact on its delivery. Localized delivery would enhance PDT, while minimizing whole-body delivery and skin photosensitivity.

Materials and Methods

Materials

Redaporfin™; 5,10,15,20-tetrakis(2,6-difluoro-3-*N*-methylsulfamoylphenyl)bacteriochlorin was provided by Luzitin, SA (Coimbra, Portugal). Gantrez® S-97 (PMVE/MA) a co-polymer of

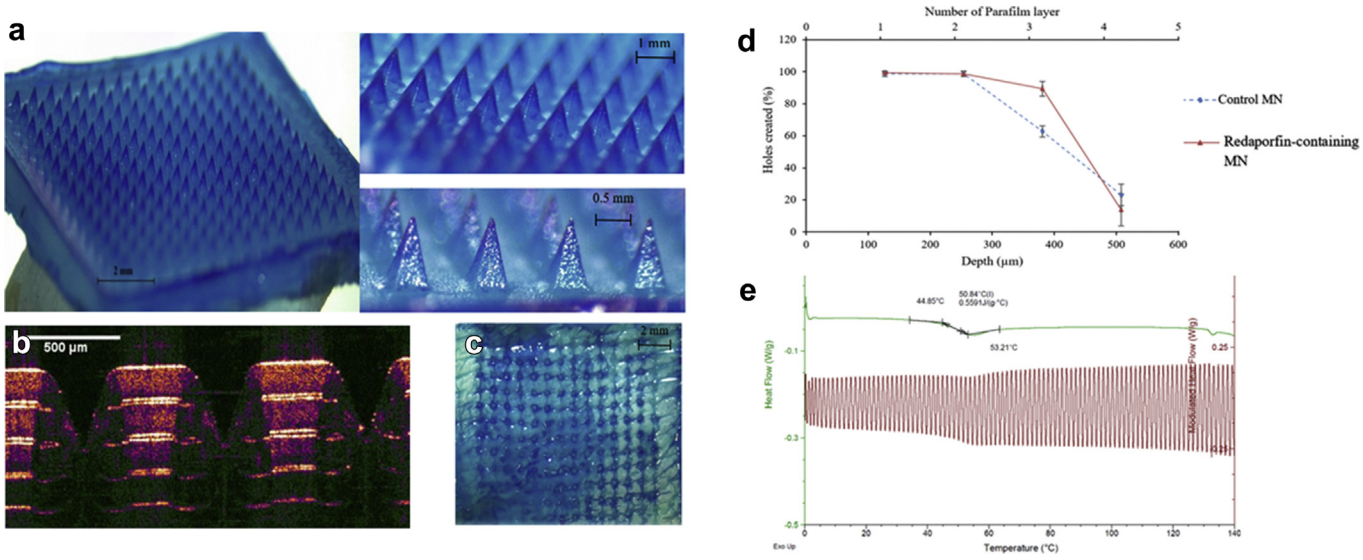

Figure 1. Physical characterization of MN arrays: (a) Light microscopic images showing methylene blue-dyed MN arrays used in the MN array insertion experiment into full-thickness neonatal porcine skin. (b) Optimal cutting temperature media image following MN array insertion into Parafilm™. Images were obtained using an EX1301 OCT Microscope. (c) Light microscopic image showing the created holes in full-thickness neonatal porcine skin following the insertion of methylene blue-dyed MN arrays. (d) Line graph showing the percentage of holes created in Parafilm™ layers following the insertion of MN arrays using the Texture Analyser with a force of 11 N. Means ± SD $n = 3$. (e) DSC thermograph of Redaporfin™-containing MN array at a drug loading of 10% w/w, which shows a Tg at ~50°C. Ramp was 3°C/min, modulation temperature was 0.8°C, modulation was 30 s, and nitrogen flow rate was at 50 mL/min.