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Permeable PDMS microneedles for the delivery of traditional Chinese medicine elemene

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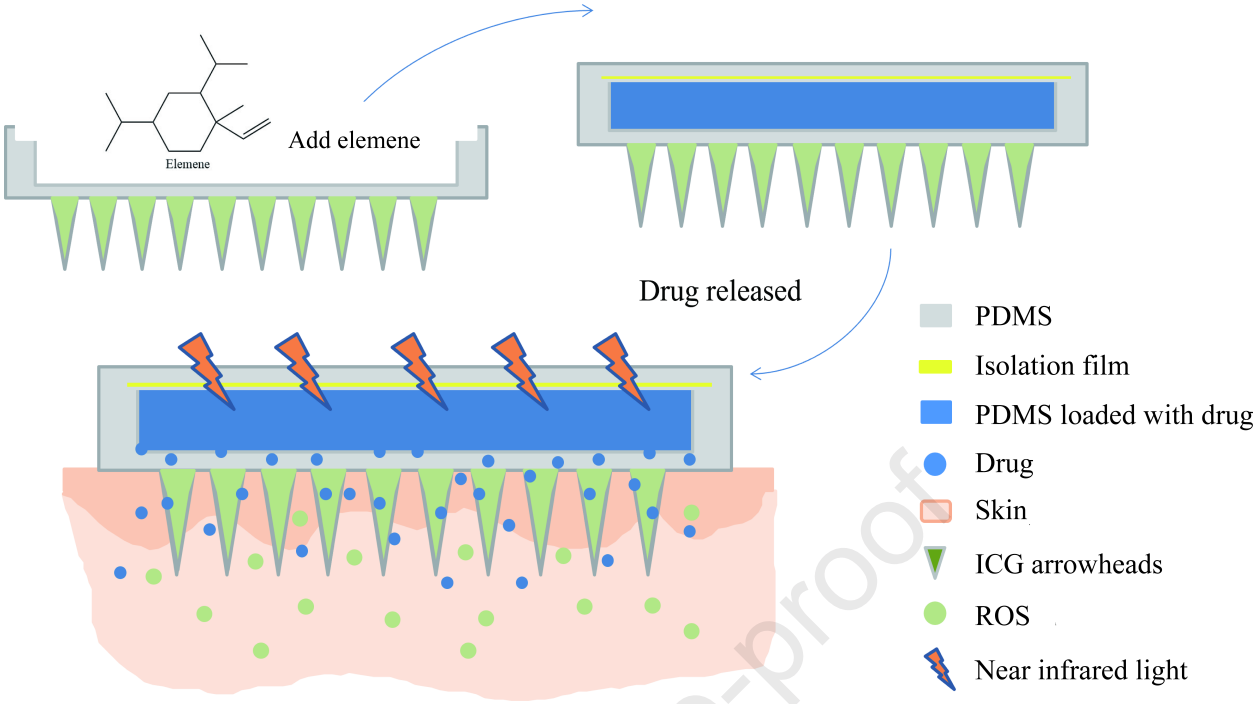

Permeable polydimethylsiloxane microneedles for the delivery of traditional Chinese medicine elemene

Microneedles (MNs) have attracted increasing attention as a transdermal delivery system (TDDS) [1]. However, traditional volatile Chinese medicines cannot be dissolved in conventional soluble MN materials, such as hyaluronic acid and chitosan, making it difficult for many traditional Chinese medicine ingredients to be applied to MN. Elemene (ELE) was successfully isolated from *Curcuma longa,* and has numerous antitumor and curative effects [2]. ELE injection and oral emulsion have been used; however, the insoluble and volatile characteristics of ELE restrict its use in MN. Consequently, it is significant to design a novel MN delivery system for traditional volatile Chinese medicine. We adopted polydimethylsiloxane (PDMS) (Dow Corning, Midland, MI, USA), a new hydrophobic silicone biomaterial with high elasticity and full transparency that forms molecular pores in molecular bonding and crosslinking, and has good air and vapor permeability [3]. When we loaded ELE onto the basement of the MNs, it could diffuse into the skin through the pores of PDMS to play an antitumor role. Furthermore, phototherapy has been developed with the benefit of good transparency. Herein, we found an MNs matrix material, PDMS, capable of transporting ELE and prepared an ELE-photosensitive MNs (ELE-MNs) to achieve drug co-administration and improve the therapeutic efficacy of drugs (Fig. S1). Materials and methods are shown in the supplementary information.

Three groups of PDMS with thicknesses of 0.34, 0.97, and 1.89 mm were prepared for diffusion experiments to verify the ability of ELE to penetrate the PDMS materials (Fig. S2). According to the ELE standard curve (Table S1) and screened receiving solution (Fig. S3). As depicted in Figs. 1A−C, we detected β-ELE (National Institute for Food and Drug Control, Beijing, China) using high-performance liquid chromatography (HPLC) in three groups at 2 h of the first sampling time point, indicating that ELE can permeate the PDMS wafer. The amount of ELE permeated by the PDMS wafers gradually increased with time in the 6-mL receiving solution, laying the foundation for the fabricating of PDMS MNs.

Comparing the ELE penetration within 8 h revealed that ELE could effectively penetrate the three groups of PDMS with varying thicknesses (Fig. 1D). The ELE amount in the transdermal diffusion receiving solution gradually increased as the thickness of the PDMS decreased. The amount of ELE permeated by 0.34, 0.97, and

1.89 mm of PDMS reached 8.43, 5.20, and 1.81 mg, respectively, at 8 h. The experiment demonstrated that ELE could penetrate PDMS; the thinner the thickness of PDMS, the stronger the ELE penetration.

Herein, we fabricated a two-layered MN system via a two-step casting process (Fig. S4). Each array consists of 100 (10 × 10) conical needles with a length of 1000 nm and a distance of 1000 nm between the tips (Fig. S5).

PDMS monomers A and B were used as the MN matrix material. The weight ratio of A to B was tested at 10:1 and 5:1, according to the complete MNs array. The mixing ratio of PDMS monomers A and B was select as 10:1 (Fig. S6). To avoid ELE volatilization, we designed drug-loading grooves to embed ELE in the backing layer of PDMS MNs (i.e., ELE-MNs). To increase the drug load of ELE, we prepared different weight ratios of the PDMS mixture and ELE (5:1, 10:1, and 20:1). Compared with the 20:1 drug-loaded ELE-MNs, the 10:1 drug-loaded ELE-MNs released higher amounts of drugs (Fig. S7). Furthermore, the MN body prepared at this ratio was complete, and the drug coating effect was satisfactory. Therefore, the PDMS-ELE mixture at a mass ratio of 10:1 was the embedding condition of ELE.

PDMS MNs have good light transmittance, and ELE penetration in them was better at higher temperatures (42 ℃) (Fig. S8). Therefore, we combined the developed ELE-MNs with indocyanine green (ICG) (J&K Chemical, Shanghai, China) and embedded them at the tip of the MN at a ratio of ICG:PDMS = 1:50 (ICG-ELE-MNs) (Fig. S9). Under near-infrared (NIR) light, ICG in ICG-ELE-MNs converts light energy into heat energy and releases reactive oxygen species (ROS), facilitating drug release and tumor treatment (Fig. S10).

To investigate the puncture ability of the MNs on the skin, we used a stereomicroscope to observe the morphological changes in the MNs tips against static force (Fig. S11A). As displayed in Figs. S11B and C, the tips of MNs became increasingly bent after loading 10 g (0.098 N) to 500 g (4.9 N), but the tips did not break. Simultaneously, using weights to apply pressure, the MNs left a clear and complete array on the pigskin surface. This result demonstrates that the prepared MNs are robust and difficult to break.

In relation to the transdermal delivery of ELE, our findings indicate that a

minimal quantity of the drug was detected at 2 h, which gradually increased with time, as evidenced by the ELE standard curve (Table S1). The increase in drug release gradually leveled off after 16 h and began to decrease at 22 h. The maximum drug amount released in the process was 49.01μg (Fig. 1E). The ELE-MNs patch could successfully deliver the drug ELE through the skin.

To investigate the drug delivery ability of MNs *in vivo*, we selected healthy nude mice of appropriate age to administer ELE-MNs into their abdomens. As demonstrated in Fig. 1F, ELE was detected in the blood samples, and the drug concentration could reach 0.8 μg/mL at 24 and 48 h. The experimental results demonstrated that ELE-loaded ELE-MNs could penetrate the skin of nude mice, reach the dermis, and enter the blood circulation.

To investigate the antitumor effect of ELE transdermal delivery by ELE-MNs and ICG-ELE-MNs, we injected B16 cells subcutaneously into female C57BL/6 mice to establish a melanoma-bearing model. Animal studies were approved by the Animal Ethical and Welfare Committee of Hangzhou Normal University (Hangzhou, China), and performed ethically following the National Institutes of Health Guide for the Care and Use of Laboratory Animals (HSD20211206).

After treatment, the tumor volume and weight in the ELE-MN, ICG-MN, and ICG-ELE-MN groups were significantly lower than those in the other groups (Figs. S12A−C); accordingly, ELE-MN and ICG-ELE-MN successfully delivered ELE to the tumor site and exhibited anticancer effects. In the weight change curve of tumor-bearing mice (Fig. S12D), the weight of mice in each group did not change significantly during administration, indicating that the treatment method of ELE delivery using the MN transdermal system in this experiment was relatively safe and effective.

In summary, two-layer ELE-ICG-MNs consisting of ICG tips and an ELE basement were successfully prepared for melanoma treatment by combining chemotherapy. These results demonstrated the antitumor effects of ELE-MNs and ELE-ICG-MNs and confirmed that the prepared MNs inhibited tumor growth and could be a potential system for effective ELE delivery for melanoma therapy.

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Figure caption

Fig. 1. Drug release in polydimethylsiloxane (PDMS) and elemene (ELE)-microneedles (MNs) *in vivo* and *in vitro*. (A) Drug release in group 0.34-mm polydimethylsiloxane (PDMS) tablets within 8 h. $^{*}P < 0.05$, 2 h compared with 4 h; $^{**}P < 0.01$, 2 h compared with 6 and 8 h. (B) Drug release in group 0.97-mm PDMS tablets within 8 h. $^{*}P < 0.05$, 2 h compared with 4, 6, and 8 h. (C) Drug release in group 1.89-mm PDMS tablets within 8 h. $^{*}P < 0.01$, 2 h compared with 6 and 8 h. (D) Total drug penetration of three groups of PDMS with different thicknesses in 8 h. $^{*}P < 0.05$, 0.34-mm PDMS compared with 1.89-mm PDMS. (E) *In vitro* percutaneous drug release by ELE-MNs. (F) Drug content was detected in mouse plasma at 24 and 48 h. Data are presented as mean ± standard deviation (SD) ($n = 3$).

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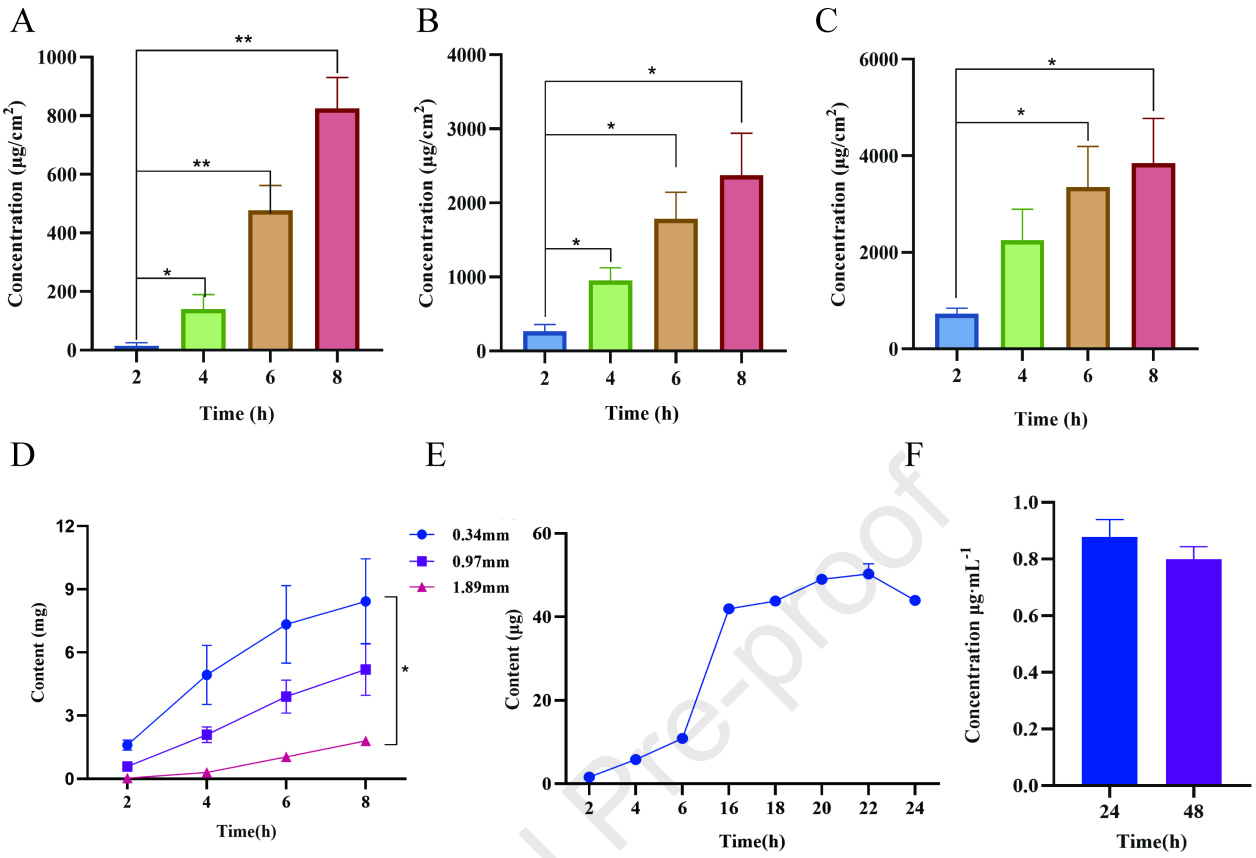

Highlights

- We designed a two-layer microneedle containing indocyanine green and elemene.
- The volatile tranditional Chinese medicine were combined with the gas permeable material PDMS to promote the transdermal release.
- This work's MNs enrich the new dosage form of the anticancer drug elemene.

Declaration of competing interest

The authors declare that there are no conflicts of interest.