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Development of sinomenine hydrochloride-loaded polyvinylalcohol/maltose microneedle for transdermal delivery

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ABSTRACT

The microneedle array of sinomenine hydrochloride(SH) was prepared by casting method using polyvinyl alcohol (PVA) and maltose (MT). The microneedle array was inserted into the foil and rat's skin to evaluate the mechanical property. Its in vitro permeation was examined to calculate the accumulation osmolality and permeation rate. In the in vivo transdermal penetration studies, blood samples were obtained to determine the concentrations of SH in plasma after administrated by SH-loaded MT/PVA microneedle array and SH-loaded hydrogel, and the pharmacokinetic parameters were determined. The average grade of irritation was calculated to evaluate the level of irritation. The developed microneedle arrays were strength enough to insert into the foil and rat's skin. The permeation rate was stable within 48h after microneedle array administration in vitro. The in vivo transdermal penetration studies of SH-loaded hydrogel and SH-loaded MT/PVA microneedle arrays showed the date of in vivo pharmacokinetic parameters. Such as, their AUC_{0-t} and AUC_{0-inf} were 5.38 ± 0.53 μg (mL h)$^{-1}$ and 35.35 ± 1.27 μg (mL h)$^{-1}$, 5.75 ± 0.49 μg (mL h)$^{-1}$ and 45.36 ± 2.36 μg (mL h)$^{-1}$, respectively. Skin irritation test showed that microneedle array has slight irritation to the rat skin. These results indicated that the SH-loaded PVA/MT microneedle array may be an ideal approach to achieve a transdermal delivery for SH.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the joints, with proliferation of the synovium and progressive erosion of cartilage and bone [1,2]. RA may lead to significant disability and consequently a reduction in patients' quality of life.

Sinomenine (7,8-didehydro-4-hydroxy-3,7-dimethoxy-17-methyl-morphinan-6-one) is an alkaloid found in the root of the climbing plant *Sinomenium acutum*. Sinomenine hydrochloride (SH, $C_{19}H_{24}ClNO_4$ Fig. 1) is widely used in clinical and has a significant anti-inflammatory, anti-immune, analgesic effect [3–5]. Oral administration of SH may lead gastrointestinal irritation and first-pass effect [6]. Some transdermal formulations have been successfully developed to overcome these problems, and the early research had confirmed the feasibility of transdermal delivery [7–9].

Transdermal drug delivery system is limited to a narrow range of compounds that easily pass through the skin. Although chemical enhancers and mechanical abrasion can increase drug permeation, they may irritate or cause damage to the skin [10]. Therefore, the challenge of creating an effective transdermal delivery system involves breaking the skin barrier for drug transport without irritating the skin.

Microneedle inserts the stratum corneum of the skin without touching the dermis and neuronal cells. It was reported for the first time that the solid microneedle arrays applied to transdermal drug delivery systems in 1998 [11]. Microneedle arrays are composed of tens to hundreds of needle-like structures which are 10–2000 μm of length. It is produced by microfabrication processes. Most of the developed microneedles are made of metal, silicon, and polymer. Recently, polymeric microneedles made from biodegradable or dissolving polymers have received considerable attention [12–16].

In this study, MT was added into PVA microneedle to enhance the mechanical property. At the same time, MT dissolves quickly

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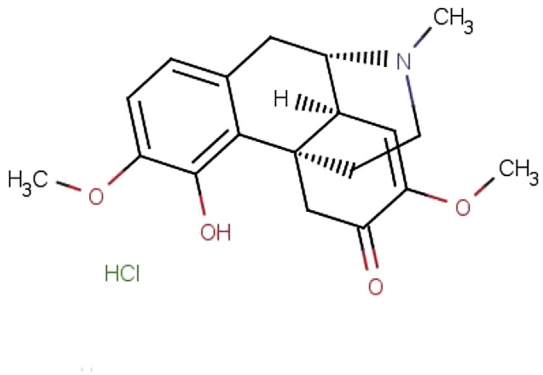

Fig. 1. The chemical structure of sinomenine hydrochloride.

form microholes for drug release. SH-loaded MT/PVA microneedle array was prepared by casting method. The mechanical properties, in vitro penetration, in vivo percutaneous absorption kinetics and skin irritation were investigated.

2. Methods

2.1. Materials

Polyvinyl alcohol (PVA) was purchased from Sinopharm Chemical Reagent Co.,Ltd (Shanghai, China). Maltose (MT) was purchased from LanJi Science and Technology Development Co., Ltd (Shanghai, China). Sinomenine hydrochloride (SH) and reference substance were purchased from ManSiTe Biotechnology Co., Ltd (Chengdu, China). Redware molds were gift from the Shanghai Jiaotong University. Ultrapure water used in the experiments was from a Milli-Q biocel purification system (UPI-IV-20, Shanghai UP Scientific Instrument Co., Shanghai, China). All other chemicals and solvents were of reagent grade or better.

Wistar rats (240–250 g) and rabbits (1.4–1.8 kg) that were supplied by the Experimental Animal Center of Anhui Medical University (Anhui, China). All animal experiments were performed in compliance with the Animal Management Rules of the Ministry of Health of the People's Republic of China (document number 55, 2001) and the guidelines for the Care and Use of Laboratory Animals of our university.

2.2. Microneedle fabrication

To serve as the microneedle matrix, in the first place, PVA was added to water(50 mL) and swollen for 24 h, then it was heated to a molten state, MT and drug were mixed in it. At last, they were cast into the redware mold and suction filtered for 20 m. After several tests and analyses, it had been evidenced that SH-loaded MT/PVA microneedle arrays which prepared by MT30% (w/w), PVA62% (w/w) and SH8% (w/w) had the best formability and a better mechanical strength to insert into the foil and rat's skin. The microneed arrays were demolded easily after the molten mixture freezed at −18 °C and thawed at 25 °C for 3 times. Finally, the microneed arrays are dried for 12 h at 75 °C (Fig. 2). In this way, a complete microneedle array would be obtained to be used in all characterization studies.

2.3. Characterization of microneedle array

2.3.1. Appearance

The prepared microneedle array was observed by electron microscopy. The length of each microneedle and the distance between them will be determined.

2.3.2. Mechanical property studies

To evaluate the mechanical property, the microneedle arrays were inserted into the foil and rats skin in vitro and in vivo, respectively. The inserted in vitro and in vivo skin were stained with methylene blue and cleaned with isopropyl alcohol to observe whether the microneedle arrays penetrated into the skin of rats clearly [17]. The preparation of the in vivo rat's skin was that the abdomen of normal Wistar rats were denuded with 8% aqueous solution of sodium sulfide and cleaned up with low concentration of NS. The preparation of the in vitro rat's skin was mentioned above. To observe the microscopic morphology of topical skin, the in vitro skin had been penetrated by microneedle arrays for 1 m at first, then stained with hematoxylin – eosin, and mounted with phosphate – glycerol at last [18]. Then it was observed with an electron microscope.

2.4. In vitro percutaneous release studies

The rat's skin was penetrated by SH-loaded MT/PVA microneedle arrays and fixed in the middle of the modified Franz diffusion cell. The accumulation osmolality-time curve was investigated to calculate the accumulation osmolality and permeation rate of drug.

2.4.1. Preparation of the in vitro rat's skin

The abdomen of normal Wistar rats were denuded with 8% (w/w) aqueous solution of sodium sulfide and cleaned up with low concentration of normal saline (NS). Those rats were killed by cervical dislocation after feeding 48 h, then cut the abdominal skin off, removed the subcutaneous fat, cleaned up with low concentration of NS, and stored at −18 °C until used.

2.4.2. Percutaneous release studies

Rat's skin was penetrated by SH-loaded MT/PVA microneedle arrays (1 g), then fixed between the supply room and the receiving room of the modified Franz diffusion cell. Stratum corneum was toward the supply room and sealed with plastic wrap. 8 mL phosphate buffer (pH = 6.8) was injected into the receiving room. Franz diffusion cell was placed at 37 °C water bath. 1 mL of the

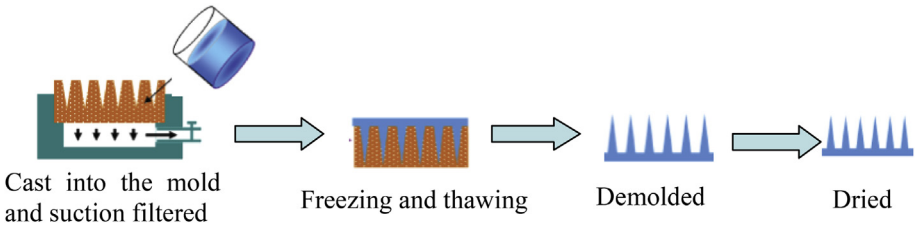

Fig. 2. The basic process of microneedle fabrication.