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# The Effects of Different Density Microneedles on Melatonin Release*

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**Abstract**

The effect of different microneedles (MNs) densities on drug release was studied by using silk fibroin with good biocompatibility as the substrate of microneedles. The mixture of D-sorbitol and silk fibroin at the ratio of 2:10 was poured into a polydimethylsiloxane mold. After vacuum extraction, constant temperature and humidity drying, the silk fibroin microneedles were obtained. Three kinds of microneedles arrays of different densities were prepared with the area of 1 $cm^2$: 5×5, 10×10 and 20×20. The length of silk fibroin microneedles was controlled at about 600 μm, and D-sorbitol/silk fibroin blend film was used as the control group. Melatonin was selected as the model drug and three kinds of MNs and blend film were used to study the drug release in vitro experiment. The aggregation structure of D-sorbitol/silk fibroin MNs was measured by X-ray diffraction (XRD) and infrared spectroscopy. The anti-compression properties of three kinds of MNs were measured by texture analyzer (TMS-PRO). The results showed that: (1) D-sorbitol could change the silk fibroin from random coil structure to the crystal structure of Silk I, and the dissolution rate of Silk fibroin MNs was low and the swelling property of silk fibroin was certain. (2) All three types of MNs have good compression resistance and puncture performance. It can effectively open the channels for drug delivery and relieve pain. (3) All three types of MNs have good drug release properties. As the density of the MNs increases, the drug release rate and cumulative drug release rate increase. As the density of the MNs increases, the compression performance of the MNs is improved. All three types of silk fibroin MNs have good penetration effects and can achieve slow-release effects. Compared with silk fibroin film without MNs, silk fibroin MNs can significantly increase the drug release rate by opening skin micropores.

*Keywords*: Silk Fibroin; MNs; Drug Release; Melatonin; Crystal structure

## 1 Introduction

Cocoons are mainly composed of silk fibroin (SF) and sericin (SS). The silk fibroin content is 72∼81%, and the silk fibroin content is 20∼30%. Silk fibroin has the characteristics of high

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mechanical strength, good flexibility, light weight, and good biocompatibility [1, 2]. Silk fibroin has α-helical conformation, β-sheet conformation, β-angle conformation and random coil conformation. The uncrystallized silk fibroin has an irregular coil-like conformation. The crystalline structure of silk fibroin is mainly divided into two types: Silk I and Silk II [3, 4].

Transdermal Drug Delivery Systems (TDDs) or Transdermal Therapeutic system (TTS) is a method for the absorption of drugs through the skin. The drugs are absorbed through the skin and enter the human blood circulation to achieve effective blood drugs. Concentration, to achieve disease treatment or prevention, a new way of administration [5]. The advantage is that the drug entering the human body is not altered by the changes in the digestive tract environment, and the constant and slow action of the drug, avoiding other rapid management methods caused by the concentration of high blood pressure caused by adverse reactions, and avoiding the first impact through the liver [6]. MNs have been widely studied as a tool of the 3rd generation transdermal system (TDDS). In recent years, many drug-loaded MNs have entered clinical trials and will soon be used for disease treatment It is a painless alternative to invasive subcutaneous injections and does not irritate nerve endings in the skin tissue, improving patient compliance at the level of pain relief. The potential risks of subcutaneous injection can be avoided by using polymer MNs [7]. Most MNs do not need to rely on the help of instruments and can be carried in a drug library for drug delivery [8, 9]. Compared with the traditional transdermal patch, MNs create many micron-sized holes on the skin surface to increase the penetration of drugs. This transdermal drug delivery method eliminates the barrier of the cuticle layer of the skin and breaks the limitation that the transdermal drug delivery system is only suitable for small molecule lipophile drugs [10, 11].

As a kind of natural polymer with non-toxic, non-irritating, good stability and excellent mechanical properties, silk fibroin is expected to become an excellent MNs substrate [12]. Zhu P Yin et al. [13] studied a kind of drug delivery system of swelling silk fibroin MNs. Using silk fibroin with good biocompatibility as the substrate of the MNs and using mold casting method, a kind of silk fibroin MNs with good swelling property, low solubility, good compression resistance and good transdermal drug release effect was obtained.

At present, the relationship between MNs density and drug transdermal release effect is unclear. In order to explore the relationship between MNs density and drug release rate, melatonin was a model drug to establish three different array densities of silk fibroin MNs in this paper. In this paper, silk fibroin film without MNs was used as a control group, and D-sorbitol and silk fibroin were mixed in a ratio of 2/10 to prepare MNs with a certain swelling property and low solubility loss [14]. It is hoped that through the study of MNs patches with different array densities, relevant experimental results can be obtained, which can provide some references for the application of silk fibroin MNs.

# 2 Materials and Methods

## 2.1 Experimental Materials

Home cocoon shell silkworm silk biological technology Co., Ltd. (Suzhou), anhydrous sodium carbonate, sodium bicarbonate, potassium dihydrogen phosphate, twelve hydration disodium hydrogen phosphate, sodium chloride, potassium chloride (national medicine group chemical reagent Co., Ltd.), D-sorbitol (Jiangsu argon krypton xenon materials technology Co., Ltd.), melatonin,