CONFERENCE PROCEEDING

Recent Development of Hyaluronic Acid Based Hollow Microneedle for Transdermal Drug Delivery - A Review

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ABSTRACT

Trypanophobia - the fear of needles. According to studies, 20% of the population has a general fear of needles or injections, with 10% of this group suffering from extreme trypanophobia. To overcome this problem, scientists from all over the world have proposed the development of painless microneedle (MN) that mimics a mosquito bite and is designed to replace traditional hypodermic needles. These conventional hypodermic needles penetrate deep into the human skin because the needles are very large pin size, which can be challenging for point-of-care diagnostic procedures. This study aims to give a brief overview on the best quality and effective MN for transdermal drug delivery (TDD), materials used as well as improved manufacturing methods. Aspects discussed in this research include painless and ultrasharp MN, fabrication using biodegradable polymers, and cost-effective production. Hyaluronic acid based hollow MN possesses many of the traits stated above and can be fabricated using Microelectromechanical systems (MEMS) or 3D Printers. It is expected that the structure, biocompatibility, and low cost of hyaluronic acid based hollow microneedle makes it highly attractive to be used for transdermal drug delivery (TDD) procedures in the medical field.

Keywords: *hollow microneedle, painless, transdermal drug delivery, biocompatibility, cost-effective*

INTRODUCTION

The skin which consists of an epidermis, a dermis, and a hypodermis is not only the largest organ of the body, but also serves as the first barrier before anything enters the body. Understanding the structure and function of the skin has encouraged scientists to further explore the development of a drug delivery system through the skin, called Transdermal Drug Delivery (TDD). TDD is a painless method of systemic drug delivery by applying a drug formulation to intact and healthy skin and has been clinically approved since 1981. TDD is the third largest drug delivery system after oral delivery and injection, and is used as an alternative approach to avoid the significant limitations associated with oral drug delivery. The drug first penetrates through the stratum corneum and then the deeper epidermis and dermis without accumulating in the dermal layer. Once a drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation.

In TDD, microneedles (MN) have proven to be the most preferred device because they are efficient, safe, comfortable, and most importantly, painless. In recent years, MNs have been widely used to deliver drugs, genes, proteins, RNA, vaccines and have produced amazing therapeutic effects. In fact, MN were firstly introduced to replace hypodermic needles, which are widely used due to its high-dose and effective method of delivering various types of drug molecules. However, the clinical use of this method is limited due to the pain and trypanophobia associated with injection in some patients. It is estimated that about 10% of the adult population suffers from needle phobia, and it is much more common in adolescents between 5 and 16 years of age (Mdanda *et al*., 2021). Different patients of different ages and genders may experience potential complications when handling a hypodermic needle, such as intramuscular pain, poor compliance, inadequate infection control, difficult venous access, and inadequate IgG levels (Berger, 1982).

MNs can be broadly classified on the basis of the delivery profile or the material used for manufacture. Morphologically, MNs used for drug delivery are classified into five types, namely solid MNs, coated MNs, dissolving MNs, hydrogel MNs and hollow MNs (Nagarkar *et al*., 2020). This study has identified hollow MN as the most suitable MN since it consists of qualities that are highly desirable. Recent reports show that this type of MN has a higher drug delivery capacity compared to solid, coated and dissolving MN arrays used to deliver chemicals, proteins and vaccines into the skin. In addition, the fabrication is simple, incurs minimal costs, and the release of drugs from the liquid preparation can be precisely controlled. Moreover, the fabrication of hollow MN using hyaluronic acid has improved the efficacy of the method in TDD procedures. Some notable advantages of hyaluronic acid include its excellent water solubility, biocompatibility, biodegradability and mechanical properties which can be very useful in developing dissolvable type carrier systems.

Therefore, hyaluronic acid based Hollow MN being the successful drug delivery system cited in this review have shown immense potential to be used for transdermal drug delivery (TDD) in the medical field.

MATERIALS AND METHODS

Preparation of the hyaluronic acid based MN

The hyaluronic acid-based hollow MN is prepared by mixing deionized water and granulated sodium hyaluronate to obtain a concentration of 5% sodium hyaluronate. The mixture is then stirred and degassed to produce gelatinous hyaluronic acid (Terashima *et al*., 2020). A polylactic acid (PLA) core is attached to the bottom of a Petri dish and filled with hyaluronic acid.

Preparation of the cylindrical and conical shape core

The fabrication method in 2.1 requires a core. Therefore, PLA is used as the main material of the core because it has high mechanical strength and affinity for hyaluronic acid. The PLA core was fabricated by stretching a PLA sheet melted by heat (Yang *et al*., 2017). Then, silicon (Si) wafer, cycloolefin polymer Nippon Zeon Co (COP) sheet, and PLA film are successively placed on the bottom plate of the experimental apparatus and the bottom plate is heated. The movement and heating of the lower plate is stopped when PLA columns have reached the set length. The lower plate is cooled with water and is lowered further.

A PLA core is attached to the bottom of a petri dish and filled with hyaluronic acid and dried at room temperature for 48 hours. The hyaluronic acid hollow array is formed by releasing some of the hyaluronic acid from the core.

The PLA columns prepared are peeled off from the COP film and then attached to the bottom plate. The bottom plate is further lifted and the bottom of the Si wafer is brought into contact with the PLA column. Thereupon, the heating of the bottom plate begins. When the set temperature is reached, the lower plate is lowered by heating and the lower ends of the PLA columns are extended to sharpen them. These are then cut off and the conical cores with hyaluronic acid were fabricated.

RESULTS AND DISCUSSION

The fabricated hollow hyaluronic acid microneedle has sufficient mechanical strength to penetrate the surface of artificial skin. The fabricated hyaluronic acid microneedles immediately dissolved/expanded when water was passed through them, so it was possible to continuously pass water through the needles by using the biocompatible material.

This microneedle has an inner hollow diameter of 50 µm. Therefore, we can use the morphology of the mosquito proboscis, with a hollow inner diameter of about 40-100 µm, It allows easier and more painless penetration into human skin. Due to its extremely delicate size, it not only does not leave permanent marks on human skin. It can also serve as a reference for further development of hollow hyaluronic acid-based microneedles.

CONCLUSION

A painless, cost-effective and ultra-sharp MN using biodegradable polymers has been successfully developed. Therefore, hyaluronic acid based hollow microneedles having all the desired traits makes it particularly appealing to be used in medical treatments for transdermal drug delivery (TDD).

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