Influence of Microneedle Structure on Improving Skin Penetration

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Abstract. Because of the advantages of painless and minimally invasion, it has attracted more attention. The microneedle piercing the skin's stratum corneum to deliver drugs into the skin is considered as the optimal choice. The research and development on penetration skin are reviewed. The influence factors of piecing skin are discussed including Needle insertion phases, Piecing force during insertion and microneedle geometry. The interaction between microneedles and skin is affected by many parameters including needle geometry, tissue characteristics and insertional methods. The microneedle geometry is considered as one of the main factor of affecting whether the skin can be penetrated effectively or not.

Introduction

Microneedle administration is a minimally invasive technique. In current experimental studies, micron-sized silicon, metal, glass, and polymer microneedles have been manufactured. Microneedles for transdermal drug delivery have attracted more and more attention because it can provide with painless, minimally invasion and time-release drug delivery. However, it is difficult to produce a qualified microneedle with high mechanical strength, small trama, and good biocompatibility. Silicon microneedles have sufficient hardness, but they are brittle. While polymer microneedles are soft to insert into the skin and tend to buckle. How to effectively penetrate the microneedles into the skin has become a hot topic of research, and it is also an important research direction for the development of microneedle technology.

The skin structure is divided into epidermis, dermis and subcutaneous tissue. The stratum corneum, which is the outermost layer of the epidermis, is the main barrier. It has a thickness of about 20 μm. The skin's stratum corneum is the tissue layer with the greatest hardness of the skin, and its elastic modulus is 6-8,900 MPa, which is also affected by the surrounding temperature and humidity. By analyzing the structure of the skin, it is noted that there is no pain if the microneedle does not reach the tissue nerve of the skin.

Research and Development on Penetration Force

Davis et al. [1] conducted the experimental and theoretical analysis of the penetration force and the broken force for the penetration into living skin. It was found that the relationship between penetration forces into the skin and transect of the needle tip is approximately linearly proportional. The fracture forces of the microneedle increase with the increase of the wall thickness and angle of the microneedle needle, and the curvature radius of the needle tip.

Paik et al. [2] used a combination of finite element simulation and experiment to study the ability of single crystal silicon microneedles with different pinpoint shapes to resist buckling failure. Aoyagi et al. [3] found that there is severe stress concentration in the contact area of the skin during penetration of the microneedles. This concentration of stress facilitates penetration of the skin, and the sharper the stress concentration of the microneedles becomes, the more obvious the stress concentration becomes. Slender and sharp microneedles are good for piercing but prone to buckling failure. Okamura et al. [4] found that the force of a needle piercing the soft tissue is closely related to the
shape of the needle tip. If the needle tip is as an isosceles triangle, an oblique triangle, and a cone separately, the piercing force gradually decreases.

Park et al. [5] conducted tests on the breaking strength of polymer micro-needles during penetration and found that the fracture strength of microneedles increases with the increase of the elastic modulus of the material and the diameter of the microneedle but decreases with the increase of microneedle length. According to their studies, when the elastic modulus of the microneedle material is less than 1 GPa, the microneedles will cause buckling failure before piercing into the skin. Wilke et al. [6] studied the effect of transverse shear force on the fracture behavior of single crystal silicon microneedles. It was found that single crystal silicon will produce shear failure along the (111) direction of the crystal surface. The crack resistance of the microneedles is affected by the length of microneedles. The closer to the tip, the lower the cracking strength is. And the average shear strength of the single crystal silicon microneedles tested is about 11 MPa, which is far lower than the limit of the silicon cantilever beam. Shibata and Kawashima et al. [7] analyzed the mechanical behavior of silica microneedles when they penetrated into cells and discussed the influence of lateral forces on stress and strain of microneedles. Khanna et al. [8] conducted an experimental study on the failure mode of cylindrical silicon microneedles. They pointed out that the simple compression failure of the microneedle when penetrating the skin does not occur, and the shear force was the cause of microneedle destruction. Lee et al. [9] used a controlled drawing technique to fabricate microneedles that can be dissolved in the body itself. The material was maltose. The length and tip diameter were 1200 μm and 60 μm respectively. Microneedles penetrated the skin and dissolved 20 minutes later.

The above research shows that the material, geometry and sizes of microneedle have the important influence on the mechanical properties of the microneedles, but the design of the microneedle geometry parameters cannot be simply based on the strength and stiffness of the microneedles themselves. Li et al. [10] found that most microneedles in a microneedle array with a length of 200 μm could not penetrate the skin and would have a large elasticity or even a viscous deformation due to penetration into the skin.

Materials of Microneedles

The materials of microneedles mainly include silicon, metal, and polymers. Since microneedle arrays are used in the biological field, it is particularly important whether microneedle materials have biological or not. The materials that can be used to prepare for microneedles are: 1. L-polylactic acid (PLLA), mainly consists of corn, potato as raw material; because of good biocompatibility and good thermal stability, it is an ideal polymer material. 2. Polystyrene (PS), which is with high rigidity, corrosion resistance, good geometric stability and very good biocompatibility; 3. epoxy resin, which is of good mechanical properties, strong adhesion, curing low shrinkage, stable chemical and physical properties, and high temperature resistance; 4. Polydimethylsiloxane (PDMS) contains of good biocompatibility and excellent elasticity, which is easy to bind a variety of materials.

The Influence Factors of Piecing Skin

When the microneedle penetrates the skin, it receives pressure from the skin. When the microneedle pieces the skin, the microneedles will undergo the pressures at axial and lateral and bending force. The microneedle can be considered as a cantilever beam to be studied. Microneedle piercing the skin will receive resistance from the skin. The following is the analysis of the process of microneedle penetration into the skin.

Needle Insertion Phases

During the insertion of the needle into the soft tissue, the interaction of the microneedle with the surrounding tissue needs to be considered. By observing the relative position of the needle to the tissue boundary, it can be divided into three basic stages of interaction, as shown in Figure 1.
The first stage: The boundary displacement (Figure 1b) begins when the needle encounters the tissue boundary and ends when the tissue boundary breaks. This phase is called a puncture event.

During the boundary displacement phase, the tissue boundary moves under the influence of the load applied by the needle tip, but the tip does not penetrate the tissue (the needle moves with the boundary). At certain point, the relative speed began to increase, indicating that a rupture occurred. As described by Shergold and Fleck [12], the puncture event and the post-puncture phase can be described by fracture mechanics theory. As the needle goes to tissue boundaries, the load at the needle tip increases, and the stress in the tissue surrounding the contact area also increases. Once these pressures exceed a certain critical value, the tissue will begin to crack, and the needle will begin to penetrate the tissue. Once the crack begins, the second phase begins.

The second stage: The insertion of the needle tip (Fig. 1c) begins when the tissue border is destroyed and ends when the tissue border slides from the tip to the shaft. At this stage, as the needle advances, the cracks in the tissue boundary expand.

The third stage: The process of insertion of the tip and shaft (Fig. 1d) begins after the second stage and ends when the needle will stop or encounter a new (internal) tissue boundary. At this stage, the contact area between the tip and the tissue and the size of the hole at the boundary remain unchanged. As the needle advances, the area of contact between the shaft and the tissue increases.

At this stage, the needle is subjected to cut force at the tip, and at the same time, the contact area between the shaft and the tissue increases, which cause increased friction.

**Piecing Force during Insertion**

In the process of piercing the skin, the microneedle is mainly subjected to a bending force perpendicular to the needle body and a compressive force parallel to the needle body. The bending force causes microneedle to bend laterally, and the compressive force in the axial direction causes the axial compression of the microneedle. When the microneedle pieces the surface of the skin, it is subjected to the bending force, and it will have relative lateral movement with the stratum corneum. At this time, it can be considered as a cantilever beam with one end fixed and the other end subjected to lateral force. In addition, the microneedle will be subjected to axial compressive force when it penetrates the skin. According to the theory of pressure rod instability, the critical compressive force can be calculated.

**Microneedle Geometry**

The geometry of the microneedle has an important influence on the puncturing force during insertion. The results show that the triangular cross-section and the larger diameter needle will increase the puncture force, which can be attributed to the large cross-section of the triangle and the large
diameter. So, the resistance to the needle tip is greater. The study on geometry of microneedle can help to optimize needle design and provide better guidance for doctors.

The microneedle array is to pierce the stratum corneum to form a channel suitable for the transmission of drug molecules on the skin surface. In order to enable the microneedle to penetrate the stratum corneum smoothly, the needle tip of the microneedle must be sharp enough. The small tip area can reduce the penetration force of the microneedle. In order to reduce pain when the penetration of the microneedle, the length of the microneedle should not penetrate the subcutaneous tissue layer of the skin. The height of the microneedle is required to be 200~500μm.

Discussion

The mechanism of transdermal delivery by microneedles is the penetration of microneedles into the stratum corneum to allow the drug through the stratum corneum. The structure design of the microneedles need to consider (1) the longitudinal force during penetration into the skin. The lateral force is very small and can be ignored; (2) The force that microneedle can withstand more than that needed to pierce the skin.

The difference of the microneedles in materials and structures not only leads to different processes, but also makes differences in the manner and efficiency of drug delivery. However, no matter how different the properties are, the microneedles must satisfy the following conditions at the same time: (1) The force of needle penetration into the skin must be small enough to be painless and minimally invasive; (2) The microneedles must have sufficient strength and stiffness to ensure that the microneedles will not break or buckle during application; (3) Microneedle must also have good biological compatibility.

The geometric factors that affect the smooth penetration of the microneedles into the skin include the radius of the microneedles, the wall angle of the microneedles, and the wall thickness. These factors are particularly important for the microneedle arrays to efficiently penetrate the stratum corneum. The analysis of the interaction between the microneedles and the biological tissues is very important for the rational design of the structure of the microneedles, and it is also a key factor affecting the penetration of the microneedles into the skin and improving the penetration of the drugs. Therefore, how to reasonably design the structure of the microneedles to effectively pierce the skin is an effective way to improve the efficiency of the transdermal drug delivery system. An excellent design of microneedle needs a thorough understanding of the mechanical properties of the microneedle itself and the structure of the skin.

Summary

The geometric factors that affect the smooth penetration of the microneedles include the radius of the microneedles, the wall angle of the microneedles, and the wall thickness. The geometry of the microneedle is very important for the improvement of the efficiency of transdermal delivery of drugs. The efficiency of transdermal delivery of microneedles can be improved through optimal structure.

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