Study on transdermal drug delivery with microneedle array

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Abstract. New pathways of drug administration have being explored because there exist weaknesses in the traditional drug delivery such as either potential degradation in the gut in oral method or pain and infection resulted from transdermal injection. Transdermal drug delivery (TDD) is a promising technology for drug administration. Among TDD, Microneedles (MNs) made transdermal drug delivery easier and more effective. The development of microneedles is necessary to eliminate or reduce the problems employing conventional needles such as pain, needle-stick injuries or needle re-use. In order to explore the drug delivery in human tissues, we made the hypothetical models of the flow of drug and to depict the flow and the moving ways of drugs. The delivering properties of drugs into skin tissue are analysed by adopting the previous hypothetical models. The results showed that the exiting velocity from the microneedle array played an important role to impact the efficiency of drug delivery. The large exiting velocity would accelerate the transdermal drug delivery and prompt drug into the circulation. In addition, the diffusion can be ignored due to a little influence.

1. Introduction
Transdermal drug delivery has more benefits to traditional approaches of drug delivery like oral administration or needle injection due to non-invasive delivery. The first-pass effect of drug in human organs will reduce the curative effect in oral pathway, and the other method, transdermal injection, the infection and pain, that reduce patient compliance, would be occurred. Currently, drug delivery employing microneedles is a new technology to deliver the drug into skin tissue. This technique has promising perspective owing to painlessness and no first-pass effect of drug. Nevertheless, the mechanism of administration needs further study.

The mechanisms of drug delivery with microneedles into tissue is still unclear hitherto because of difficult measurement. In order to make sure the mechanism of drug delivery in tissue, we tried to build hypothetical models of the flow of drug and to describe the drug flow. The skin, which is made of water and solid particles, can be considered as a porous medium. The drug flow advances in the skin tissue along the passing way from microneedles and diffuses along the route from higher concentration gradient to lower one. During the transportation of drugs, the issue would take up a part of drugs, another part would be absorbed by capillary, and the others will would full the interval space of the tissue. During spreading, the tissue of skin can be separated into two areas, saturated and unsaturated. The two areas are separated by a moving border (interface). Through analysis on moving border (interface) and progressing velocity of drug liquid, we can observe the relationships among impacting factors such as moving border interface, initial and propagating velocity and to depict and forecast the propagation of dispersed drugs.
When ultrasonic wave spreads in liquid medium, there exists alternating circle of positive and negative pressure [1]. Due to the alternating tension and extrusion force of ultrasonic wave, the density of liquid will change constantly. During the negative pressure period, the density of liquid will decrease obviously because of the effect of tensile force. While in the positive pressure period, the density of liquid will increase gradually as the increase of extrusion force. When the intensity of ultrasonic wave is large enough, the strength of tension pressure becomes very large. The strong pulling force will increase the distance between liquid molecules. When the distance between molecules exceeds the critical molecular distance, it is equivalent to the local fracture of liquid medium, which will form a small void, namely the cavitation effect [1].

Under the action of ultrasound, the cavitation bubble expands and shrinks continuously, but the condition of non-breaking is steady-state cavitation, which is the main type of bubbles in living tissues. When the ultrasonic energy is large enough, the cavitation bubbles will continue to grow and collapse rapidly after several oscillation cycles, and implode, resulting in local high temperature and pressure, accompanied by very strong shock wave and high-speed micro-jet, which is called transient cavitation [1].

Cavitation effect is very important to enhance the skin’s permeation. It can destroy and change the structure of tissue and cell, increase the gap between tissue and cell, form water way between tissue and cell, and then increase the permeability of skin tissue and cell. Ultrasound cavitation effect is the most important mechanism of ultrasound-induced permeation. Transient cavitation is the main one.

2. Theoretical principle

At present, most of the quantitative studies on the effect of ultrasound seepage enhancement are carried out through experiments. In the course of the experiment, the changes of blood drug concentration or other physiological reaction parameters after drug entering human body reflect the effect of ultrasound on osmotic enhancement. Some researchers also observed the micropore density of skin tissue and the radius of micropore in the tissue after ultrasound, and analyzed the effect of ultrasound on promoting osmosis [1].

According to the research needs, the following hypothesis is made: in the process of ultrasound-induced infiltration, the pressure, ambient temperature, viscosity coefficient and density of liquid in subcutaneous tissue are stable. Cavitation effect in subcutaneous tissue is only related to ultrasound parameters. The complex motion of cavitation bubbles in subcutaneous tissue is simplified to the growth and collapse of cavitation bubbles.

According to the above hypothesis, a physical model is established: there is a single bubble in the infinite liquid (tissue fluid). During the process of movement, the cavitation bubble keeps spherical all the time, and its central position is fixed, only the wall of the cavitation bubble moves radially. The gas inside the cavitation bubble is uniformly distributed. The effects of gravity and pressure in bubbles are not taken into account [2].

According to the motion equation of cavitation bubble, namely Rayleigh-Plesset equation [3], the relationship between the radius of cavitation bubble and the frequency and intensity of ultrasonic wave is established. The change of bubble radius reflects the change of bubble wall. Through the simulation of the change of the cavitation bubble wall, the relationship between the effect of ultrasound seepage enhancement and the frequency and intensity of ultrasound was obtained. The derivation process is as follows:

In the physical model, the preliminary radius of the bubble is $R_0$, the viscous coefficient of tissue fluid is $\mu$, the surface tension coefficient is $\sigma$, the static pressure of the tissue fluid is $P_0$, the pressure of the gas is $P_{g0}$, and the vapor pressure is $P_v$, the superficial tension of the cavitation bubble of the initial state is obtained. For $2\sigma/R_0$.

Suppose that the ultrasonic sound field is $P_A(t)$. At the initial moment, the force acting on the cavitation bubble wall by the ultrasonic sound field is positive pressure, then the excitation sound field can be expressed as:

$$P_A(t) = -P_g \sin(2\pi f_s t)$$

(1)
The equation of motion of cavitation bubble wall can be further improved as follows:

\[
\frac{R}{t^2} \left( \frac{\partial^2 R}{\partial t^2} \right) + \frac{3}{2} \left( \frac{\partial R}{\partial t} \right)^2 = -\frac{1}{\rho} \left[ (P_0 + \frac{2\sigma}{R_0}) \left( \frac{R}{R_0} \right)^3 - P_A \right] - \frac{2\sigma}{R} - P_0
\]

\[
+ \frac{R}{\rho c \eta} \frac{\partial}{\partial t} \left[ \left( P_0 + \frac{2\sigma}{R_0} \right) \left( \frac{R}{R_0} \right)^3 - P_A \right] - \frac{4\mu}{\rho R} \frac{\partial R}{\partial t}
\]

(2)

The ultrasonic excitation signal in formula (1) is substituted into equation (2), and the relationship between ultrasonic frequency and intensity and the motion state of cavitating bubbles is obtained. Then, the movement curve of cavitation bubbles in tissue fluid is obtained by solving with MATLAB.

3. Simulation

In order to get the effect of frequency and intensity of ultrasound on the cavitation effect, the parameters of these factors are fixed in the next analysis of this paper although other factors also affect the results of cavitation effect. Then the calculation and simulation are carried out. Here, tissue fluid density \(\rho = 1000\, \text{g} \cdot \text{m}^{-3}\), sound velocity \(C = 1416\, \text{m/s}\), static pressure \(P_0 = 1.013 \times 10^5\, \text{Pa}\) and surface tension coefficient \(s = 0.076\, \text{N/m}\) were taken.

In the study of the influence of ultrasound frequency, the control variable method is used to make the intensity of ultrasound unchanged, which is 1.25 times the static pressure of tissue fluid, i.e. \(P_a = 1.25 \times 10^5 P_0\), and the acoustic field stimulated by ultrasound is equation (1). In the past studies of cavitation effect, the radius of cavitation bubbles observed by experiments is generally between 5 and 10. In the micron range, therefore, in this study, the initial radius of cavitation bubble \((R_0 = 6\, \mu\text{m})\) is calculated, and its resonance frequency is 650 KHz. When the ultrasonic frequencies are 20KHz, 60KHz, 200KHz, 600KHz and 2MHz respectively, the variation of the radius of the cavitation bubble in a period is obtained by taking the parameters into account and simulating them with MATLAB (for convenience of analysis, the longitudinal coordinate is \(R/R_0\), i.e. the ratio of the radius of the cavitation bubble to the initial radius), as shown in Figure 1(a)-(e), respectively.

As can be seen from Fig. 1, when the ultrasonic frequencies are 20KHz, 60KHz, 200KHz, 600KHz and 2MHz, the ratio of the maximum radius to the preliminary radius \(R(t)_{\text{max}}/R_0\) of the cavitation bubble is 7.3574, 3.7657, 2.3149, 1.5061 and 1.1032, respectively. Based on the above results, the maximum radius ratio \(R(t)_{\text{max}}/R_0\) of cavitating bubbles is plotted as a function of frequency, as shown in Fig. 2 below.

![Curves](image1.png)

**Figure 1.** Curve of \(R(t)/R_0\) in a period
From Figure 1, it can be seen that the maximum radius of ultrasonic cavitation bubbles decreases gradually with the increase of ultrasonic frequency when the intensity of ultrasound is constant in the subcutaneous tissue, which also leads to the decrease of the time required for the bubbles to complete a single expansion and contraction. That is to say, the time required for cavitation bubbles to vibrate and collapse gradually decreases. It can be seen that when the frequency of ultrasound is 20 KHz, the time required is about $5.0 \times 10^{-5}$ s; when the frequency of ultrasound is 60 KHz, the time required is about $1.6 \times 10^{-5}$ s; and when the frequency of ultrasound is 200 KHz, the time required is about $5.1 \times 10^{-6}$ s. When the frequency of ultrasound is higher than the resonance on bandwidth frequency of bubbles at 650 KHz, the time required for the expansion and contraction of cavitation bubbles becomes very short. In such a short time, the cavitation bubbles begin to be compressed before they expand sufficiently large. Therefore, at this time, the cavitation bubbles can only oscillate around their initial state without collapsing. The collapse phenomenon, as shown in Figure 1. When the frequency is 2 MHz, the ratio of the maximum radius of the cavitation bubble to the initial radius is only 1.1032, which is basically equal to the initial radius. Therefore, if the frequency of ultrasound is used, the effect of ultrasound seepage promotion is poor. It can also be seen from Figure 2 that the ratio of the maximum radius to the preliminary radius of the ultrasonic cavitation bubble decreases with the increase of the ultrasonic frequency while the ultrasonic intensity remains unchanged. Therefore, the frequency of ultrasound should not be too high when using ultrasound to promote infiltration.

Figure 2. $R(t)/R_0$ of cavitation bubbles

Figure 3. Changes of $R(t)/R_0$ in 10 cycles
When the influence of ultrasonic intensity is studied, the frequency of ultrasound is unchanged. Here a resonant frequency is 650KHz, the acoustic field stimulated by ultrasound is equation (1), the static pressure in tissue fluid is $P_0$, and the initial radius of cavitation bubble is $R_0=6\mu m$. When the ultrasonic intensity is $0.5P_0$, $5P_0$, $10P_0$ and $20P_0$ respectively, the variation of the radius of the ultrasonic cavitation bubbles in 10 cycles is obtained by taking the parameters and simulating them with MATLAB (for convenience of analysis, the longitudinal coordinates are still $R/R_0$, i.e. the ratio of the radius of the cavitation bubbles to the initial radius), as shown in Figure 3(a)-(d), respectively.

From Fig. 3, it can be seen that the ratio of maximum radius to initial radius $R(t)_{max}/R_0$ is 1.508, 3.701, 4.551 and 6.219, respectively, when the ultrasonic frequency is constant and the ultrasonic intensity is $0.5P_0$, $5P_0$, $10P_0$ and $20P_0$, respectively. The maximum radius ratio of cavitation bubbles varies with the ultrasonic intensity $P_a$ under different ultrasonic intensities, as shown in Fig. 4 below.

![Figure 4. $R(t)_{max}/R_0$ of cavitation bubble with ultrasound intensity $P_a$](image)

It can be seen from Fig. 3 and 4 that when the ultrasonic frequency is resonant, the maximum radius of the ultrasonic cavitation bubble increases with the increase of the ultrasonic intensity. With the increase of ultrasonic intensity, the time required for the expansion and contraction of cavitating bubbles increases gradually. As shown in Fig. 3, when the ultrasonic intensity is $5P_0$, the time required is about $0.2 \times 10^{-5}s$, when the ultrasonic intensity is $10P_0$, the time required is about $0.28 \times 10^{-5}s$, and when the ultrasonic intensity is $20P_0$, the time required is about $0.32 \times 10^{-5}s$. When the intensity of ultrasound is less than the hydrostatic pressure of tissue fluid, the maximum radius of the ultrasonic cavitation bubble is 1.508 times of the initial radius. The cavitation bubble can not expand to a large enough size to collapse, and can only maintain the oscillating state of continuous expansion and contraction. The reason for this phenomenon is that when the intensity of ultrasound is high, the forces acting on the cavitation bubbles are relatively larger, and the kinetic energy obtained is more, which makes the bubbles expand and contract faster, and because of the larger kinetic energy, the cavitation bubbles can grow to a large enough radius to reach the collapse state.

Through the analysis above, it can be seen that the larger the maximum radius of bubble expansion to collapse, the higher the energy of shock wave and micro-jet generated by collapse, and the radius of ultrasonic cavitation bubble when the frequency of ultrasound is low, while the higher the frequency of ultrasound is, the higher the radius of ultrasonic cavitation bubble is. It is not enough to make the cavitation bubble collapse, but to maintain the vibration state near the initial radius. That is to say, the transient cavitation effect is main in low-frequency range, while the steady-state cavitation effect is dominant in high-frequency range. Therefore, the effect of low frequency ultrasound on the penetration of drug solution in skin epidermis and dermal tissue layer is better. Under other conditions unchanged, when the ultrasonic intensity is high, the ultrasonic cavitation bubble can obtain more energy, thus the maximum radius of expansion to collapse is larger, and the energy of shock wave and micro-jet generated by collapse is higher; and when the ultrasonic intensity is low, the energy of ultrasonic cavitation bubble is less. Steady-state cavitation will occur. Therefore, ultrasound with higher intensity can promote the penetration of drug solution in tissue better.

Based on the analysis, it can be seen that the effect of penetration promotion is better when the frequency of ultrasound is low. Therefore, low-frequency ultrasound with frequencies of 20 KHz to 60 KHz is selected to improve the penetration efficiency. For the ultrasonic intensity, although the
greater the intensity, the better the effect of penetration promotion, but too high the intensity will
damage the skin tissue structure, so choose the ultrasound intensity of 2 W/cm² to 10 W/cm².

4. Conclusion
The important mechanism in the process of sonopheresis, ultrasonic cavitation effect, is introduced.
Simplifying the process of ultrasound-assisted infiltration, a mathematical and physical model of
ultrasonic cavitation bubble movement process is established in subcutaneous tissue, and the
mathematical and physical model is simplified and analyzed. The influence curve of the frequency and
intensity of ultrasound on the movement of the bubble wall was obtained by using MATLAB
simulation, and the influence of the frequency and intensity of ultrasound on the effect of ultrasonic
seepage enhancement was analyzed. The appropriate frequency and intensity of ultrasound for
ultrasonic osmosis are selected.

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