SONOPHORESIS DEVICE WITH SINGLE FLAT FLEXTENSIONAL TRANSDUCER DEVELOPED FOR ULTRASOUND ENHANCED TRANSDERMAL DRUG DELIVERY SYSTEM

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Abstract

A sonophoresis device with a flat flextensional ultrasound transducer is proposed. The optimum diameter, thickness and material types of vibration plate are simulated by FEM. The proposed flat flextensional ultrasound transducer has been fabricated and its characteristics are investigated. The simulation results of first resonance frequency and deformed profile obtained from FEM are compared with the experimental results which showed a reasonable agreement. When this proposed sonophoresis was operated at its first vibration mode by applying AC voltage 80 V, the transmission acoustic intensity, which was calculated from measured vibration velocity and transmission coefficient equation, reaches to 32.05 mW/cm².

Key Words
sonophoresis device, flat flextensional transducer, ultrasound, transdermal drug delivery.

1. Introduction

Ultrasonic transducers play important role in nondestructive testing systems, ultrasonic machining technology, ultrasonic welding instruments, and ultrasonic imaging and diagnostic systems. Recently, ultrasound enhanced transdermal drug delivery technology (sonophoresis) has received increasing attention. The current use of ultrasound to deliver drugs is its use in physical therapy for non-invasive treatment. Research in the last two decades has dramatically increased the understanding of ultrasound and its effects on skin and transport of pharmaceutical agents.

The proposed dominant mechanism of sonophoresis, although not completely understood, has been suggested to be the result of cavitation [1-2]. Low frequency ultrasound has the capability to produce micro-bubble in the liquid and tissue. These investigators have suggested that the cavitation bubbles disrupt the lipid bilayers and allow the drugs or molecules pass through the stratum corneum. With sonophoresis, significant enhanced transportation of model drugs such as insulin and mannitol has been verified by using commercial sonicator.

Development of sonophoresis devices of varying types of transducers have been patented, such as the namely horn type and disk type. The major drawback in drug delivery is the large size and weight of the conventional ultrasound transducer devices. For practical reasons, the application of ultrasound enhanced transdermal drug delivery, a lighter and simple sonophoresis device is necessary.

In this paper, the sonophoresis device with a flat flextensional ultrasound transducer, which was often used as ultrasonic distance / obstacle sensors and transducers for telephonic application [3], was designed and fabricated as a tool to generate the ultrasound under the water for transdermal drug delivery application. In comparison with the traditional seven classes of flextensional transducers [4], which have complicated design and structures, the flat flextensional transducer has simple structure and its fabrication processes are easy and inexpensive for mass-production.

2. Structure of the sonophoresis device

2.1 Design structure

In this sonophoresis device, a ring-shaped piezoelectric material and a piece of vibration metal membrane were bonded together. The flat flextensional transducer was usually supported at the periphery and vibrates at its first flexure vibration mode. The whole flat flextensional ultrasound transducer was assembled onto a rigid stainless steel body. The height of the body is decided by the sonophoresis experimental setup. In this proposed structure of the sonophoresis device, a holding rod is
attached to the threaded hole so the sonophoresis device is
submerged in the donor compartment as shown in Fig. 1.

Figure 1. Schematic structure of the sonophoresis device and the experiment setup.

2.2 Simulation structure and mode analysis

Ultrasound frequency at a range of 20 to 100 kHz has
been shown to enhance transdermal transport of a variety
of drug molecules. The enhancement is determined by
various parameters, including intensity, duty cycle and
application time. The most important parameters are
ultrasound frequency and acoustic intensity applied on the
skin surface [5]. Previous research work showed that
significant transdermal transport of model drug such as
insulin (MW=6000 Da) has been conducted using 20 kHz
commercial sonicator operating at intensities from 12.5-
225 mW/cm² [6]. Therefore, the sonophoresis device
should be operated at its first vibration mode at frequency
similar to the commercial sonicator (i.e. 20 kHz) with
intensities that have been shown to transdermally deliver
drugs such as insulin. From this point of view, in order
to design the proposed structure as shown in figure 1, the
following sizes must be determined: the thickness $t_p$,
inner and outer diameter ($d_i$ and $d_p$ respectively) of ring-
shaped PZT, and the thickness $t_m$ and diameter $d_m$ of the
vibrating zone of the metal vibration membrane as shown
in Fig. 2.

The finite element method (FEM) was used for vibration
mode analysis of this flat ultrasound transducer and the
key parameters were determined. The bottom surface of
the device is submerged in liquid during the experiment
as shown in the figure 1. The coupling between metal
vibration membrane and liquid elements was considered
in the simulation work. In order to simplify the
calculation procedure, standard sized ring-shaped PZT
was selected and only the parameters of various types of
material were changed to determine the structure of the
transducer. The material type of the metal vibration
membrane of the flexextensional transducer should have
high Young’s modulus and electrical conductivity and
most importantly, it is non-corrosive to atmosphere and
chemicals. The material data and the simulation results
are shown in Table 1 and Table 2, respectively. Figure 3
shows the detailed simulation structure with the material
type identifications of different elements and first
vibration mode of the transducer.

Figure 2. Simplified simulation structure of the sonophoresis device with the flat flexextensional ultrasound transducer and the
key parameters.
Figure 3 (a) Simulation model representing a half of the sonophoresis device. ‘1’ denotes ring-shaped PZT; ‘2’ denotes metal vibration membrane; ‘3’ denotes stainless steel body; ‘4’ denotes interface elements between fluid elements and structural elements; ‘5’ denotes interface elements between fluid elements and skin; ‘6’ denotes interface elements between fluid elements and glass wall; and ‘7’ denotes fluid elements without structural elements. (b) first vibration mode of the transducer.

Table 1. Material constants

<table>
<thead>
<tr>
<th>Material type</th>
<th>Yong’s modulus (N/m²)</th>
<th>Poisson’s ratio</th>
<th>Density (kg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stainless steel</td>
<td>20.7 × 10¹⁰</td>
<td>0.3</td>
<td>7.86 × 10³</td>
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<td>Brass</td>
<td>10.06 × 10¹⁰</td>
<td>0.35</td>
<td>8.55 × 10³</td>
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<td>Aluminum</td>
<td>7.06 × 10¹⁰</td>
<td>0.345</td>
<td>2.7 × 10³</td>
</tr>
<tr>
<td>Titanium</td>
<td>12.02 × 10¹⁰</td>
<td>0.361</td>
<td>4.5 × 10³</td>
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<tr>
<td>Tungsten</td>
<td>41.1 × 10¹⁰</td>
<td>0.28</td>
<td>19.3 × 10³</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>32.48 × 10¹⁰</td>
<td>0.293</td>
<td>10.2 × 10³</td>
</tr>
</tbody>
</table>

Table 2. Simulation results of key parameters and first resonance frequency

<table>
<thead>
<tr>
<th>Material type</th>
<th>d₁ (mm)</th>
<th>d₂ (mm)</th>
<th>t₁ (mm)</th>
<th>d₃ (mm)</th>
<th>t₄ (mm)</th>
<th>f₁ (kHz)</th>
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</thead>
<tbody>
<tr>
<td>Stainless steel</td>
<td>6.0</td>
<td>12.0</td>
<td>1.2</td>
<td>16.0</td>
<td>0.4</td>
<td>20.14</td>
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<td>1.2</td>
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<td>0.4</td>
<td>17.66</td>
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<td>1.2</td>
<td>16.0</td>
<td>0.4</td>
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<tr>
<td>Molybdenum</td>
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<td>1.2</td>
<td>16.0</td>
<td>0.4</td>
<td>21.58</td>
</tr>
</tbody>
</table>

3. Fabrication

The piezoelectric ring-shaped material (C-203, Fuji Ceramic, Tokyo, Japan) has a thickness 1.2 mm with inner diameter and outer diameter 6.0 mm and 12.0 mm, respectively. The piezoelectric ring was poled in the thickness direction. The silver electrode on the piezoelectric ring was first ground with sandpaper to remove the oxide layer and then clean with acetone. Based on the simulation results as shown in Table 2, the first resonance frequency of the proposed flexitensional transducer with stainless steel is approximately 20 kHz.

The stainless steel sheet was cut to size using the wire cut EDM machine for the prototype device (a single station stamping tool can be used to obtain the vibration metal membrane in the future) and ground with sandpaper. The piezoelectric ring was then bonded to the stainless steel vibration membrane. The bonding material was electrically conductive silver epoxy (Acoustic technologies, Singapore). The thickness of the bonding layer was approximately 20 μm. The whole assembly was cured in the oven for 75 minutes at 130 °C and then kept at room temperature for 24 hours. The entire structure of the sonophoresis device after fabrication is shown in Fig. 4(b).
4. Experiment results

4.1 Resonance frequency

As mentioned in the section 2.2, the flat ultrasound transducer is to be operated at its first resonance frequency in which the electrical and mechanical energy transformation rate is the highest among its rest resonance frequencies. The vibration frequency was measured by laser scanning vibrometer (Polytec GmbH, Waldbronn, Germany) and the experiment setup is shown in Fig. 4(a). The square-shaped scan area was selected in which there were 323 scanning points. According to the simulation result as shown in Table 2, the bandwidth of the sweep frequency was set to start from zero and end at 50 kHz. The data of each scanning point was transferred to the analysis software Polytec PSV 7.11 and the result is shown in Fig. 5. The first resonance frequency is 17.406 kHz a little bit smaller than that of simulation result (20.14 kHz).

4.2 Vibration velocity and mode shape

In general, the acoustic intensity is proportional to the square of the vibration velocity and can be defined as:

\[ I = v^2 \rho c \]  

(1)

Where, \( I \) is acoustic intensity, \( v \) is surface vibration velocity of the device, and \( \rho \) is the water density and the \( c \) is the acoustic velocity in the water. The same experiment setup and configuration setting were used to measure the surface vibration velocity of the device. The device was mounted on the wall of the water tank, which contained 1 liter distilled and degassed water, and operated at its first resonance frequency (17.406 kHz) by applying AC voltage 80 V. Fig. 6(a) shows the 3D surface vibration velocity profile. The average vibration velocity analyzed with software Polytec PSV 7.11 was 42.2 mm/s and the corresponding acoustic intensity generated by the device calculated by using Eqn. (1) was 267.1 mW/cm². But, this calculated acoustic intensity, which can be considered as an incident acoustic intensity, only exists at the interface of stainless steel vibration membrane and water. The acoustic transmission coefficient is defined as:

\[ \text{Transmission coefficient} = \frac{4Z_{\text{steel}}Z_{\text{water}}}{(Z_{\text{steel}} + Z_{\text{water}})^2} \]  

(2)

Where, \( Z_{\text{steel}} \) and \( Z_{\text{water}} \) are the acoustic impedance of stainless steel and water, respectively. So the acoustic transmission coefficient is only 12% [7] because of the mismatch of acoustic impedance between stainless steel and water. Therefore, the transmitted acoustic intensity is about 32.05 mW/cm². Further experiments will be conducted to measure the acoustic intensity inside the water by using a calibrated hydrophone.

The result as shown in Fig. 6(b) was calculated from the surface vibration velocity and regenerated by the analysis system of the laser scanning vibrometer, so it is only the reference to show the deformed shape of the stainless steel membrane when the sonophoresis device vibrates. However, the 3D deformed profile as shown in Fig. 6(b) proves that when this proposed flat flexextensional ultrasound transducer works at frequency 17.406 kHz, its vibration mode is the first mode.
Figure 5. Resonance frequencies scanning results.

Figure 6(a) 3D surface vibration velocity profile. 6(b) 3D surface vibration displacement profile.
5. Conclusion

A sonophoresis device with a flat flextensional ultrasound transducer was proposed. The optimum diameter, thickness and material types of vibration plate were simulated by FEM. The simulation results of first resonance frequency and deformed profile obtained from FEM were compared to experimental results and agreed well.

The proposed flat flextensional ultrasound transducer has been fabricated and its characteristics were investigated. In comparison with the other flextensional ultrasound transducers, it has the simplest structure and its fabrication process is easy and inexpensive. When this proposed sonophoresis was operated at its first vibration mode by applying AC voltage 80 V, the transmission acoustic intensity, which was calculated from the measured vibration velocity and transmission coefficient equation, reaches to 32.05 mW/cm².

All these values and features showed that the proposed sonophoresis device is feasible for use in practical application. Further experiments will be performed to measure the acoustic intensity at a fixed distance away from the device inside the water and to test the performance of the device during the drug delivery experiments.

6. Acknowledgement

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References