Introduction to Sonophoresis and Power Design of Sonophonetic System

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Outline

- Introduction
- Transdermal Drug Delivery
- Sonophoresis
- Power System Design
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- References
Introduction
Introduction

- There have a lot of ways that make drugs entering the body. Among them, taking drugs orally is the most acceptable way to everyone. Except that, intravenous or intramuscular injections are accepted by most people.

- Other entering paths through eyes, rectum and skin are also used.

[From http://publications.nigms.nih.gov/medbydesign/chapter1.html]
Transdermal Drug Delivery
Transdermal Drug Delivery (TDD)

Transdermal drug delivery offers an attractive mode of drug administration. However, applications of transdermal drug delivery are limited due to low skin permeability.

[From http://www.nature.com]
Barrier of TDD

A unique hierarchical structure of lipid-rich matrix with embedded corneocytes in the upper strata of skin, stratum corneum (SC), is responsible for this barrier [From Ref. 4].
Enhancement of TDD

The figure shows possible mechanisms for the synergistic effects between various enhancers [From Ref. 1].
Sonophoresis
Ultrasound

Sound is our experience of the propagation of pressure waves through some physical elastic medium, such as air or liquid. Ultrasound is the frequency of the sound or vibration greater than 20 kHz.

[From http://www.compositiontoday.com]
Sonophoresis has been shown to increase skin permeability to a variety of low- as well as high-molecular weight drugs. The enhancement induced by ultrasound is particularly significant at low-frequencies.
Sonophoresis

Sonophonetic drug delivery. Drug is placed on the skin beneath the ultrasonic probe [From Ref. 2].
Factors of Sonophoresis

The enhancement induced by low-frequency sonophoresis is determined by four main ultrasound parameters:
- Frequency
- Intensity
- Duty Cycle
- Application Time
Factors of Sonophoresis: Intensity

<table>
<thead>
<tr>
<th>Category</th>
<th>Typical Intensity Range</th>
</tr>
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<tbody>
<tr>
<td>Surgical</td>
<td>$&gt;10 \text{ W/cm}^2$</td>
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<tr>
<td>Therapeutic</td>
<td>$0.5-3 \text{ W/cm}^2$</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>$0.0001-0.5 \text{ W/cm}^2$</td>
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</tbody>
</table>

Exposure intensity levels in medical applications [From Ref. 5].
Factors of Sonophoresis: Frequency

A partial summary of ultrasound frequencies used for medical applications [From Ref. 4].
Factors of Sonophoresis: Application Time

<table>
<thead>
<tr>
<th>Drug</th>
<th>Membrane used</th>
<th>Experimental conditions</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl (F) &amp; caffeine (C)</td>
<td>Human skin, in vitro</td>
<td>Fcm: 20 kHz, 2.5 W/cm², P (60 min)</td>
<td>× 34 enhancement</td>
<td>Boucoud et al. 2001[103]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cen: 20 kHz, 2.5 W/cm², P (60 min)</td>
<td>× 4 enhancement</td>
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<td></td>
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<td>Fex: 20 kHz, 2.5 W/cm², C (60 min)</td>
<td>× 4 enhancement</td>
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<td></td>
<td></td>
<td>Cef: 20 kHz, 2.5 W/cm², C (60 min)</td>
<td>× 1 enhancement</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>Pig skin, in vitro</td>
<td>20 kHz, 7 W/cm², P (10 min)</td>
<td>× 21 enhancement</td>
<td>Mitragotri &amp; Kost 2001[110]</td>
</tr>
<tr>
<td>Caffeine &amp; morphine</td>
<td>Hairless mouse skin, in vitro</td>
<td>Ccm: 40 kHz, 0.44 W/cm², C (4 h)</td>
<td>× 4 enhancement</td>
<td>Monti et al. 2001[105]</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Rats, in vivo</td>
<td>Mec: 40 kHz, 0.44 W/cm², C (4 h)</td>
<td>× 10 enhancement</td>
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<tr>
<td></td>
<td></td>
<td>20 kHz, 2.5 W/cm², P (15 min)</td>
<td>Anti-Xa activity</td>
<td>Mitragotri &amp; Kost 2001[112]</td>
</tr>
<tr>
<td>Aerosol (Ate), carboloe (Car), timolol (Tim), betaxolol (Bex)</td>
<td>Rabbit eyes, in vitro</td>
<td>Ate: 20 kHz, 2 W/cm² (60 min)</td>
<td>× 2.6 enhancement</td>
<td>Zderic et al. 2002[104]</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Pig skin, in vitro</td>
<td>Car: 20 kHz, 2 W/cm² (60 min)</td>
<td>× 2.8 enhancement</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>Rats, in vivo</td>
<td>Tim: 20 kHz, 2 W/cm² (60 min)</td>
<td>× 19 enhancement</td>
<td></td>
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<tr>
<td>EMLA cream</td>
<td>42 human subjects</td>
<td>Ilet: 20 kHz, 2 W/cm² (60 min)</td>
<td>× 4.4 enhancement</td>
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<tr>
<td>Lidocaine</td>
<td>32 healthy male volunteers</td>
<td>55 kHz, 60 min). Power 13 W RMS</td>
<td>× 10 enhancement</td>
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<td>Cisplatin A</td>
<td>Rat skin, in vitro</td>
<td>0.5 and 1 MHz, 2 W/cm², C</td>
<td>Masked decrease in glucose levels</td>
<td>Mitragotri et al. 2000[106]</td>
</tr>
<tr>
<td>Olignucleotides</td>
<td>Full-thickness pig skin, in vitro</td>
<td>Surface anaesthesia phantories group showed a significantly higher pain threshold than other groups</td>
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<td>Protease</td>
<td>Hairless mouse skin, in vitro and in vivo</td>
<td>20 kHz, 2.4 W/cm², P (10 min)</td>
<td>7-fold increase in concentration of drug in skin</td>
<td>Liu et al. 2006[108]</td>
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<td>Buprenorphine</td>
<td>60 osteoarthritic patients (target knee joint)</td>
<td>1 MHz, 1 W/cm² (5 min)</td>
<td>Successful delivery of antisense oligonucleotides</td>
<td>Tezel et al. 2004[107]</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Swine dorsal region, in vitro</td>
<td>1 and 1 MHz, 1.5 and 2 W/cm², C &amp; P</td>
<td>Highest perstration observed at 1 MHz, 20 W/cm², continuous output</td>
<td>Chung et al. 2002[106]</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>10 healthy subjects</td>
<td>3 MHz, 1.0 W/cm², P (5 min)</td>
<td>Ibuprofen phantories found to be effective and</td>
<td>Kozaroglu et al. 2003[111]</td>
</tr>
<tr>
<td>Calcitonin &amp; D3O</td>
<td>Excised hairless rat skin, in vitro</td>
<td>3 MHz, 0.2 W/cm², C (1 min/cm²)</td>
<td>generally well tolerated after 10 therapy sessions, but it was not superior to conventional ultrasound in patients with knee osteoarthritis</td>
<td>Campos et al. 2007[112]</td>
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<td></td>
<td></td>
<td>1 and 1 MHz, 1.5 and 2 W/cm², C &amp; P</td>
<td>ultrasound as effective as acetaminore and accelerator of cutaneous caffeine permatation</td>
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<td></td>
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<td>41 kHz, × 22.6 enhancement</td>
<td>Phenophoretic effect occurred with drug when its application warmed the skin</td>
<td>Saliba et al. 2007[113]</td>
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<td>158 kHz, × 6.3 enhancement</td>
<td>Calcinosis;</td>
<td>Mutoh et al. 2003[114]</td>
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<td></td>
<td>445 kHz, × 3.8 enhancement</td>
<td>41 kHz, × 22.7 enhancement</td>
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<tr>
<td></td>
<td></td>
<td>3 kHz, 1 W/cm², P (5 min)</td>
<td>158 kHz, × 6.3 enhancement</td>
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<td>0.54 W/cm², C (15 min)</td>
<td>445 kHz, × 3.8 enhancement</td>
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<td></td>
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<td>3 kHz, 1 W/cm², P (5 min)</td>
<td>3 kHz, 1 W/cm², P (5 min)</td>
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<tr>
<td>Sulfurbromide B</td>
<td>Pig skin, in vitro</td>
<td>19.6, 39.9, 58.9, 78.6 and 93.4 kHz, C</td>
<td>For each frequency applied, there was a threshold intensity below which no enhancement was</td>
<td>Tezel et al. 2001[131]</td>
</tr>
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<td></td>
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<td>0.54 W/cm², C (15 min)</td>
<td>observed; this intensity increased with frequency</td>
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<tr>
<td>Sulfurbromide B</td>
<td>Full-thickness pig skin, in vitro</td>
<td>20 kHz, 7.5 W/cm², P (10 min)</td>
<td>Ultrasound enhances surfactant delivery and dissolution</td>
<td>Tezel et al. 2002[117]</td>
</tr>
<tr>
<td>Nile red &amp; calcine</td>
<td>Full-thickness porcine skin, in vitro</td>
<td>20 kHz, 15 W/cm², P (2 h)</td>
<td>Lipid removal from stratum corneum implicated as factor contributing to observed permeation enhancement effects of low-frequency ultrasound</td>
<td>Alvarez-Roman et al. 2003[116]</td>
</tr>
<tr>
<td>Sodium fluorescein</td>
<td>Rabbit eyes, in vitro</td>
<td>880 kHz, 0.19, 0.34 and 0.56 W/cm², P (5 min)</td>
<td>× 10 enhancement</td>
<td>Zderic et al. 2003[117]</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Rat abdomen skin, in vitro</td>
<td>1 MHz, 0.5 W/cm², C (1 h) and 2 kHz, 2.5, 3.25 and 5 W/cm², P (30 min)</td>
<td>Low-frequency ultrasound resulted in higher transdermal penetration than high-frequency</td>
<td>El-Kamel et al. 2007[118]</td>
</tr>
</tbody>
</table>

The results of sonophoretic studies for drug delivery are summarised in Table [From Ref. 2].
Power System Design
Piezoelectric

Ultrasound waves are created when a generator produces electrical energy that is converted to mechanical energy through the deformation of piezoelectric material in a transducer [From Ref. 3].
Inverter

Inverter is through the semiconductor power switches on and off the role of the DC power into AC power of a transformation device.

Classification of the circuit topology:
- Push-Pull
- Half-Bridge
- Full-Bridge
**Inverter: Push-Pull**

Push-pull inverter is composed of two switches, two diodes and a center-tapped transformer with the composition [From Ref. 9].
Inverter: Half-Bridge

Mainly for low power inverter, or as a full-bridge inverter Bridge Arm [From Ref. 9].
The full-bridge inverter has two kind of patterns, 180 degree square wave pattern and PWM adjusts voltage pattern [From Ref. 9].
Pulse width modulation, or PWM, is a technique for getting analog results with digital means. Digital control is used to create a square wave, a signal switched between on and off.
Pulse Width Modulation (PWM)

Voltage spikes of one transistor and original waveform [From Ref. 8].
Snubber

Snubbers are an essential part of power electronics. Snubbers are small networks of parts in the power switching circuits whose function is to control the effects of circuit reactances.
Classification of Snubber

- Simple RC Voltage Snubber
- RCD Voltage Snubber
- Simple RL Current Snubber
- Two Terminal 3D-2C-1L Voltage Snubber
- Three Terminal 3D-2C-1L Voltage Snubber
- Three Terminal Voltage Snubber with Intermediate Voltage
- Flyback Reset Current Snubber
- Resonant Recovery Current Snubber
- Transformer Reset Voltage Clamp
Snubber: Simple RC Voltage Snubber

The simple RC snubber provides damping of the parasitic resonances in the power stage and is probably the most widely used of all snubber circuits [From Ref. 7].
Snubber: Simple RC Voltage Snubber

Original waveform (solid line) and the snubber (dotted line) [From Ref. 10].
Snubber: Simple RC Voltage Snubber

This example shows the importance of simulating and optimizing the snubber circuit using the actual components [From Ref. 6].
Snubber: RCD Voltage Snubber

The circuit in Figure A applicable to either rate of rise control or clamping. The circuit variation shown in Figure B is applicable only to the clamp operation [From Ref. 7].
Snubber: RCD Voltage Snubber

Typical snubber and clamp, the effects that these have on a representative switching waveform [From Ref. 8].
When it is important to minimize both the loss in the switch, a combination snubber, using both RC and RCD, can produce very good results with low losses [From Ref. 6].
Future Works
Future Works

- Papers
- Circuit Test
References
References

[9] 劉鳳君，“現代逆變技術及應用”，北京：電子工業出版社，2006。
[10] 張波、丘東元，“電力電子器件”，華南理工大學電力學院。