Intra-maxillary Drug delivery and Bio-sensing via Dental Implant and its considerations

Li, Yu-Jung
Lecturer of Anatomy, Physiology, and Pathology, St. Mary’s Junior College of Medicine, Nursing, and Management, Taiwan
2016. 07. 23

- Doctoral Candidate, Institute of Electronic and Mechanical Engineering, National Taipei University of Technology
- Master of chemistry, Tamkang University
- Master of biophysics, National Central University
- Master of clinical dentistry, National Yang-Ming University
- Training of oral and maxillofacial surgery in Taipei Veterans General Hospital
Table of Content

• Motivation: Current situations
• Design: 
  (1) Drug delivery module
  (2) Bio-sensing module
• Experimental results:
  (1) Glucose monitoring
  (2) Molecular pumping and delivery
  (3) Canine model for insulin therapy
• Discussions & Special considerations:
  (1) Engineering
  (2) Medical
  (3) Dental
Current situation

- **Geriatrics:** The aging population as people > 65 years in Taiwan has reached to 10.7% in 2010, and will approach to 20.1% in 2025.
- **Geriatrics:** (1) Dentistry, (2) Critical + Chronic care
- **Medical monitoring and therapeutics:**
  - (1) Non-invasive: BP, HR, RR monitoring + Oral tab
  - (2) Invasive → (A) Blood monitoring + (B) Injections into blood
- **Diabetes Mellitus (DM):**
  - (1) Triad: DM + CAD + Renal disease
  - (2) MDII: (4 One-touch blood sugar + 4 insulin injections) / Day
  - IVII: (12 One-touch blood sugar + 12 insulin injections) / Day
- **Pain origins from invasive procedures:**
  - Drug → Blood
    - **Macromolecule**: cannot pass through GI tract
    - (1) Mucosal + (2) dermal barriers
  - Proteins, functional polymers, etc.
Current situation

- **Geriatrics**: The aging population as people > 65 years in Taiwan has reached to **10.7%** in 2010, and will approach to **20.1%** in 2025.
- **Geriatrics**: (1) Dentistry, (2) Critical + Chronic care
- **Medical managements**:
  - (1) Non-invasive
  - (2) Invasive → (A) Blood monitoring + (B) Injections into blood
- **Diabetes Mellitus (DM)**:
  - (1) Triad: DM + CAD + Renal disease
  - (2) MDII: (4 One-touch blood sugar + 4 insulin injections) / Day
    - IVII: (12 One-touch blood sugar + 12 insulin injections) / Day
- **Pain origins from invasive procedures**:
  - Drug → Blood
    - (1) **Mucosal** + (2) **dermal barriers**

Thinking about molecular delivery in dentistry?
Intra-bony molecular slowly releasing: calcium hydroxide/iodoform paste (Vitapex ®) Application

2012. 10. 22
#46: Deep caries s/p reversible pulpitis
IRM indirect capping

2015. 01. 16
#46: Apical lesion s/p pulpitis; Pus (+)
Endodontic treatment

2015. 07. 16
#46: Apical lesion s/p pulpitis; Pus (-)
Calcium hydroxide RCT

2016. 01. 26
#46: Apical lesion s/p pulpitis; Pus (-)
New bone formation

38 Y/O male, Personal History: Smoking(+), Past history: Nil
Intra-bony molecular slowly releasing: calcium hydroxide/iodoform paste (Vitapex ®) Application

Notice: Periodontal ligament (PDL) exists, Patient felt mild pain as paste delivery

Hint: For dentists, intra-bony molecular delivery is more than possible, or even familiar
Table of Content

• **Motivation:** Current situations

• **Design:**
  1. Drug delivery module
  2. Bio-sensing module

• **Experimental results:**
  1. Glucose monitoring
  2. Molecular pumping and delivery
  3. Canine model for insulin therapy

• **Discussions & Special considerations:**
  1. Engineering
  2. Medical
  3. Dental
Dental implant & Pain origins

1. Traditional pain origins: (A) Pulp, (B) Periodontal ligament (PDL) → (C) Dental implant

2. Bone quality: 
   - **Maxilla:** Type III + Type IV → Rich of **bone marrow** within **blood pool**
   - **Mandible:** Type I + type II
     - 1. Cushion for injections
     - 2. Avoid from thrombosis

3. **Bicon® Implant system:** Absence of screw threads between:
   - (A) prosthetic abutment (B) Implant fixture

4. **Implant supported** (1) **Drug delivery** module, and (2) **Biosensor** module
(1) Drug delivery module

- (a) Piston
- (b) Marker
- (c) Drug container
- (d) Prosthetic abutment
- (e) Titanium Implant fixture
- (f) Canals for drug releasing

(A) Mechanical releasing

(B) Piezoelectric releasing

(C) DDS module above the titanium implant fixture with outside prosthetic crown

Piezoelectric pump
Wireless controller
Piezoelectric micro-pump design & Bluetooth 4.0

Structure of the piezoelectric pump including valves inside

Bluetooth 4.0 module with Software interface by C++
(2) Biosensor module

Biosensor placed inside the Prosthetic abutment, including:
(1) Sensor IC
(2) Bluetooth module
(3) Power supply
(4) Extend electrodes

Then the set of the electrodes Extent outside the fixture by the canals, including:
(1) Working electrode
(2) Counter electrode
(3) Reference electrode
Glucose oxidase (GOD) coating & circuit design

GOD coated over working electrode for blood sugar sensing.

\[
\beta\text{-D-Glucose} + O_2 + H_2O \xrightarrow{\text{Glucose oxidase}} \text{D-Gluconic acid} + H_2O_2
\]

The current may change corresponding to the Glucose concentrations.

The current changes are recorded by the Bluetooth 4.0 module. And then they are transferred to outside portable devices, such as computers or cell phones.
# Table of Content

- **Motivation:** Current situations
- **Design:**
  - (1) Drug delivery module
  - (2) Bio-sensing module
- **Experimental results:**
  - (1) Glucose monitoring
  - (2) Molecular pumping and delivery
  - (3) Canine model for insulin therapy
- **Discussions & Special considerations:**
  - (1) Engineering
  - (2) Medical
  - (3) Dental
Drug delivery exp.

(A) Mechanical drug delivery module

(B) Piezoelectric drug delivery module
Bio-sensing exp.

The cyclic voltammetry by different glucose concentration, sweeping from 0.2 to -0.6 V:
(A) From 50 mg/dL to 500 mg/dL.
(B) Peak value recorded and shows highly linearity, with 4 mg/dL increasing will elevate 1 μA of the current.
Preliminary canine study

Canine model: After 1 month of osseointegration, 2\textsuperscript{nd} stage surgical exposure arranged to link the drug delivery and biosensing module. The blood sugar is monitored over intra-oral biosensor and lower limb calibration.
Initially 5 unit of the NPH (rapid onset insulin) is performed. Then the blood sugar is monitoring every 5 minute from both intra-oral biosensing module and anterior lower Limbs for calibrations. Blood sugar debonding at 25th minute may be due to glucagon Releasing.
Table of Content

• **Motivation:** Current situations
• **Design:**
  1. Drug delivery module
  2. Bio-sensing module
• **Experimental results:**
  1. Glucose monitoring
  2. Molecular pumping and delivery
  3. Canine model for insulin therapy
• **Discussions & Special considerations:**
  1. Engineering
  2. Medical
  3. Dental
Discussions

- **Other invasive drug delivery device:**
  1. Short-period (<2 wks): Central Venus Catheter (CVC)
  2. Long-term: Port-A-Catheter, dental implant supported DDS module

- **Advantages of the implant supported DDS and biosensor module:**
  1. Relative painless during drug delivery (vs CVP + Port-A)
  2. Fixed by surrounding bone, avoid from component loosening, and internal bleeding (vs Port-A)
  3. Non-invasive while drug reloading & module replaced (semi-implanted)
  4. Lead to creative drug releasing and bio-sensing therapy:
     - low volume and continuous (drug releasing + blood monitoring)
  5. Free from thrombolism: Surrounding bone marrow structures

- **Diabetes Mellitus (DM):**
  As target disease due to frequently invasive therapy demanded.
  1. Biosensor: 4 mg/dL (+) lead to 1 μA increasing
  2. Drug releasing: 0.5 ml contains 5000 units insulin, meet 2 months demands

- **Myocardial infarction (MI):** CK, CKMB + troponin I continuous monitoring /5 min lasting for 1-2 months
Discussions

- **Restricts and constrains in implant supported DDS and biosensor module:**
  1. Drug delivery type, volume, and speed is restricted
  2. It is limited for patient with frequently invasive procedure demands
  3. Dental and medical cooperation is needed to ensure safety & efficiency
  4. Frequently dental appointments for device debridement & drug reload

- **Further improvement:**
  1. Module size & volume minimizing for practical applications
  2. Enzyme polymerization & improvement for long-term blood monitoring
  3. Accuracy improvement over IC design for further applications
  4. Safety concern: drug polymerization during releasing
  5. Pain evaluation experiments design
Discussions

Special considerations

**Engineering**

1. **Accuracy in monitoring:** From \( \text{mg/dl} \) \( \rightarrow \) \( \text{ng/dl} \), about \( 10^{-6} \) degree
2. **Component sealing:** Avoid infection status
3. **Size minimization:** CMOS + MEMS technology

**Medical**

- **Geriatrics:**
  - Painless
  - Non-invasive
  - Continuous macromolecular delivery
  - Frequently blood monitoring
  - (1) **Neurodegenerative disorders:** 1. Alzheimer's 2. Parkinson's disease
  - (2) **Metabolic disorder:** Diabetes mellitus
  - (3) **Cardiovascular disease:** Continuous CK + CKMB monitoring

**Dental**

- **Avoid from:**
  - (1) **Periodontitis:** Remove infective status
  - (2) **Excessive occlusal loading:** Medical purpose
  - (3) **Osseointegrative destructions:** Combined + selective releasing
    - Calcium hydroxide + iodoform
Acknowledgements

- Special thanks to Prof. Chih-Cheng Lu of National Taipei University of Technology and his advanced microsystem and device laboratory for the technological support. Valuable assistance from Prof. Jung-Tang Huang of National Taipei University of Technology is also acknowledged. This research received financial support under grants MOST 103-2221-E-027-017 and MOST 103-2218-E-027-012, Taiwan.

Reference


Mucosa VS. Skin

**Moist environment:** Saliva flow contain bacteria retain (Accumulation)

Saliva decrease (Radiotherapy origin, etc.) → Dental caries, periodontitis

Provide possibility for long-term medical device placement (ex: dental implant)

**Mucosal location:**
1. Nasal
2. Oral
3. Anal
4. Vaginal
5. Urethra

- (1) Jaw bone supported
- (2) The biggest cavity
- (3) Well studied in Dental implant
- (4) Thrombosis prevention inside bone marrow
(A) Prosthetic abutment
Within micro-pump

Dialysis chamber

Implant fixture

Semi-permeable membrane

Antibody

Coated antigen

Blood flow

Red blood cell
(1) Antibody trapping: **SLE**

(2) Molecular trapping: **Amyloidosis**

(3) Cellular trapping