Engineering Biomaterials in Advanced Therapy Medical Devices

Ragnhild E. Aune

Dept. of Materials Science and Engineering, Norwegian University of Science and Technology (NTNU), Trondheim, NORWAY
Introduction

• In the battle against medical diseases doctors have in their arsenal many powerful weapons.

• What they lack is a reliable way to obtain real-time data about the service lifetime of a particular medical device, as well as its association with patients exposure to serious side effects such as:
  ➢ an increased risk of complications (infections, thrombosis, improper healing, cell growth and mechanical failure of the device).
  ➢ decreased quality of life
  ➢ increased suffering
  ➢ prolonged hospital stay.
Overall Project Objective

- The overall aim of the project is to develop integrated and validated methodologies as the basis for appropriate:
  - risk evaluation assessment
  - patient safety assessment

in regards to clinical use of medical devices in oncology, respiratory and anesthesia/intensive care.
Multidisciplinary Approach is Needed

• Clinical and Epidemiology
• Quality of Life (QoL) and the Society/Stakeholders
• Physical and Chemical with focus on Materials Science
• Biochemical and Toxicology
• Policy and Decision Makers

In-vivo and In-vitro Approach
Physical and Chemical

Central Venous Line
Physical and Chemical

- The main questions to be answered are:
  - How does material degradation affect the performance of the medical device?
  - What are the technical problems caused by materials degradation?
  - How can the rate of decline of performance of the medical device be ensured and evaluated?
  - What should be done to ensure that performance remains far above the critical level for the entire service lifetime of the device?
  - What are the toxic problems caused by medical device degradation?
Case Study:
Chemotherapeutic-Induced Surface Degradation of Subcutaneous Venous Access Ports (SVAPs)

• To reduce the risk of complications related to SVAPs used in the administration of antineoplastic drugs to women with breast cancer (chemotherapy treatment).

In-vitro and In-vivo Settings

• Investigate the influence of:
  ➢ exposure of antineoplastic drugs on the inner surface of the catheter
  ➢ exposure of whole blood on the outer surface of the catheter
Subcutaneous Venous Access Ports (SVAPs)

- The SVAP consists of a reservoir compartment that has a silicone septum cover for needle insertion, and a polymer catheter.
- The port is surgically inserted under the skin in the upper chest (or in the arm).
- The port can be made of different polymers, medical grad stainless steel and medical grad titanium.
- The catheter material in the present study: Polyurethane

SVAP inserted through basilic vein to vena cava superior.
SVAP Complications

The use of SVAPs are often associated with an increased risk of complications.

• *Infection* - a severe bacterial infection can compromise the device and require its surgical removal.

• *Thrombosis* - formation of blood clots in the venous and/or in the catheter.

• *Mechanical failure* – the system could break, usually the attached catheter, and become lodged in the circulatory system.

Increased suffering for the patient, a prolonged hospital stay, and higher medical costs.
Experimental Set-up (In-vitro)

Simulation Chamber
• Designed to allow *in-vitro* testing of SVAPs under well controlled (steady state) conditions ⇒ temperatures (chamber and body), humidity and oxygen level, gas flow rate (inert), and flow rate of the drugs.

SVAPs
• 3 catheters were exposed to chemotherapy treatment.
• One catheter was only exposed to NaCl solution.
Medical Drugs

• In total 6 treatments was administrated in accordance with the protocol for patients treated for breast cancer ⇒ 3 FE$_{100}$C$^*$ + 3 Taxotere treatments (duration 18 weeks).

• The medical protocol adopted was calculated for the average Scandinavian women (165.5 cm in height and 64.7 kg in weight) resulting in a body surface area of 1.72 cm$^2$.

*A mixture of the drugs ondansetron, betamethasone, fluorouracil, epirubicin and cyclophosphamide
Sampling

- 3 cm long samples were taken from the end of catheters after each treatment (after 36 hours and 3 weeks*).

- The samples were rinsed with sterilized water, and stored in separate containers in a desiccator outside the simulation chamber.

- The samples were later analyzed by FE-SEM, FTIR and CAM

* Just prior to the next treatment.
In the Chandler loop experiments the blood circulation is simulated, with a rotating disc (10 rpm) placed in a water bath kept at 37°C.

The pre-exposed catheters are introduced into the loop in PVC tubes filled with whole blood from a donor.

The duration of the experiment is 60 min.
FE-SEM – Inner Surface

• Securing catheter samples throughout the treatment allows for continues evaluation of the inner surface degradation of the material as a function of the direct contact with:
  
  ➢ the liquid flow itself
  ➢ medical drugs

Duration of study 18 weeks

Exposed to 6 NaCl treatments

Noticeable surface alterations.

Exposed to 6 chemotherapy treatments
Chandler Loop – Outer Surface

• Exposing post-treated catheter samples to whole blood allows for continues evaluation of the outer surface degradation of the material.

• Visual evaluation of the catheters also reveals the degree of blood clotting formation, as well as the changes of surface morphology.


Blood clots attached to the surface.

A drastic increase in porosity.

No prior treatment

60 minutes in whole blood

After 6 chemotherapy treatment

Exposed to 6 treatments prior

Reference exposed to whole blood

x4000

10μm

1.0KV 9.4mn x4.00k SE(L)

10.0μm

1.0KV 9.5mn x4.00k SE(L)
Blood Analysis

Thrombin-AntiThrombin Analysis (TAT)

- TAT analysis allows for the evaluation of the degree of blood incompatibility of the catheter samples post-chemotherapy treatment.

Blood clotting (thrombosis) - Activation of thrombocytes (platelets) and the formation of fibrin.
Mechanical Testing

- Tensile testing of material samples allows for the evaluation of the alterations of the mechanical properties (with focus on tensile strength and toughness) of the catheter material throughout the duration of chemotherapy treatment.

Decrease in tensile strength already after one treatment.

Reference catheter - no prior treatment

Catheter exposed to 6 chemotherapy treatments

Decrease in tensile strength already after one treatment.
Ex-Implanter SVAPs (In-vivo)

• Patients included:
  ➢ Women in the age group 18 - 80 years with invasive breast cancer treated with chemotherapy.

• Factors documented:
  ➢ age
  ➢ type of chemotherapy treatment
  ➢ additional medical treatment
  ➢ complications
  ➢ duration of device implanted
  ➢ patients wellbeing/quality of life
FE-SEM – Inner/Outer Surfaces

- Ex-implanted catheters allows for:
  - evaluation of material surface alterations as a result of exposure in a patient environment.
  - comparison between in-vitro and in-vivo results
  - validation of developed methodologies for in-vitro testing
Expected Impact

• Development of comprehensive understanding of the properties, interaction and rate of the use of different medical devices in relation to quality of life, healthcare costs and the environment.

• Validated test methods / schemes for the identification of potential adverse effects from different biomaterials.

• Support to policy and decision makers concerning the clinical use of different biomaterials in respect to various stakeholders (patient, public authorities, industry, researchers and citizens).

• Support to local authorities and the European / International Committee for Standardization (CEN / CENELEC).
Thank you for your attention!

Professor Ragnhild E. Aune

ragnhild.aune@ntnu.no