Nitric Oxide Materials—A Natural Approach to Creating More Biocompatible Medical Devices

Melissa M. Reynolds
melissa.reynolds@colostate.edu

October 28, 2009

Biological Response to Implantable Materials

Before Implant

After Implant

Responses
• Tissue disruption
• Inflammation
• Infection
• Clotting
• Biofouling

Device surface

Biofilm

Fibrinous and/or tissue encapsulation
Endothelium

**Nitric Oxide (NO) – Effective Antiplatelet Agent**

**Biological Functions of Nitric Oxide**

- Nitric Oxide (NO)
- Prostacyclin
- Thrombomodulin
- Heparan

**Endothelial Cell**

- Sensors
- Grafts ECC
- Stents
- Anti-platelet action
- Anti-proliferative
- Wound healing
- Angiogenic
- Vasodilatory
- Anti-microbial
- Catheters
- Respiratory Devices
- Pharmaceuticals
- Bronchodilation
- Anti-cancer
Sources of Endogenous Nitric Oxide

De Novo Synthesis

Decomposition of S-nitrosothiols

Cu^{2+} + Asc → Cu^{+} + Asc
Cu^{+} + RSNO → Cu^{2+} + RS + NO

Two Major Functions of Nitric Oxide: Vasodilation Anti-platelet

Nitric Oxide Producing Materials Concept

Materials that produce NO at or above that of the endothelial cells will be more biocompatible
Designing Nitric Oxide Materials

Strategies for NO-producing Agents

- Proton-mediated NO release
- Photoinitiated NO release

Strategies for NO-producing Polymers

- NO agents covalently attached to polymer backbone
- NO agents in polymer blends
- NO agents in polymer blends
NO Release Agents in Polymer Blends

**Important Factors**
- Organic phase pH
- Water permeability
- Diffusion coefficients

![Blood boundary layer diagram](image)

**Tailored NO Release Profiles Using NO Release Agents in Polymer Blends**

**A. Polymer/Plasticizer Ratio**

<table>
<thead>
<tr>
<th>Polymer/Plasticizer Ratio</th>
<th>1.2 PVC/DOS</th>
<th>1:1 PVC/DOS</th>
<th>2:1 PVC/DOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO Release (10^-6 mol)</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>Time (h)</td>
<td>0</td>
<td>25</td>
<td>50</td>
</tr>
</tbody>
</table>

**B. Quantity**

<table>
<thead>
<tr>
<th>Quantity</th>
<th>8 wt. pct.</th>
<th>4 wt. pct.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO Release (10^-6 mol)</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Time (h)</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>

**C. Plasticizer Type**

<table>
<thead>
<tr>
<th>Plasticizer Type</th>
<th>NPOE</th>
<th>DOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO Release (10^-6 mol)</td>
<td>3.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Time (h)</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>

**D. Additive Type**

<table>
<thead>
<tr>
<th>Additive Type</th>
<th>KTpCPB</th>
<th>DNNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO Release (10^-6 mol)</td>
<td>4.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Time (h)</td>
<td>0</td>
<td>15</td>
</tr>
</tbody>
</table>
NO Release Agents via Covalent Attachment

Post-Loading Approach

Monomers

+ NO Agent + NO Agent + NO Agent

Pre-Loading Approach

Polymer backbone

Polyurethanes, silicone rubber, polymethacrylates, poly(vinyl) chloride, polyethylenimines

NO Release Profiles using Covalent Attachment of NO Release Agents

Post-Loading Approach

- Can vary NO production by length of NO exposure
- Limitations on temperature processes
- “Ready to use”

Pre-Loading Approach

- Can incorporate “known” amounts of NO
- Can use common manufacturing processes
- Post-treatment needed for use

Time (h)

NO Release (10^-6 mol)

1:1 chain extender : glycol

1:2 chain extender : glycol
Formation and Inhibition of Thrombus

Coagulation cascade

Platelet adhesion

Phospholipase C activation

Platelet activation

Cytoplasmic Ca\(^{2+}\) Increasing

Platelet shape change/secretion

What inhibit platelet activity?— prostacyclin and NO
What inhibit thrombin?— thrombomodulin and heparin

Combination Coatings: NO Release and Active Heparin

- Dual Action
  - Heparin
  - Nitric oxide
- Function
  - Factor Xa assay
  - Chemiluminescence

Biological Response - ECMO

*Extracorporeal Membrane Oxygenation*

**Device**

- Angiocath (Teflon) 14GA 1.16” BD
- Gish Straight Connectors
- 3/8” ID 1/4” ID 1/4” ID
- Transonic Flow Probe
- 10FR Thoracic Catheter

**Animal Model**

- Prepared circuits with various NO fluxes
- Measured NO release pre and post
- Monitored platelet consumption, ACT, and metHb


**Control ECC**

- NIH Image Analysis

**ECC Thrombus Area (pixels/cm²)**

- Control
- 25% NOrel

Post 4 hours

**NO-release surface**

- Courtesy: Dr. Robert Bartlett
- ECLS Lab, Univ. of Michigan
Response - Vascular Grafts

Parameters
- ~100 μm coating
- Gamma sterilized
- 21 day implant time
- Arterial / venous model
- NO-release for 21 days

Coating Method
- Basecoat
- NO-releasing layer
- Finishing layer

Animal Model
- Carotid Artery
- Jugular Vein

Results

<table>
<thead>
<tr>
<th>Control NO-release</th>
<th>Graft</th>
<th>TFSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>47.1±6.5</td>
<td></td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>97.8±1.5</td>
<td></td>
</tr>
</tbody>
</table>

Comparison of VEGF and NO donors to induce angiogenesis in HUVECs

Response - Angiogenesis

Conditions

Response - Sensors

Device

Dynamic Response

Biological Response

Inflammatory Response

- Subcutaneous implant of sham sensors in rats (n=8)
- 7 day study
- Measured inflammatory cell infiltration

Application: Hemodialysis system

Dialysis fluid

Blood

Dialysis membrane

© 2023 Cengage Learning. All Rights Reserved.
Summary

- Nitric oxide materials provide an alternative approach for solving biofouling
- Nitric oxide has multiple functions
- Demonstrated tailoring of NO-release properties from hydrophobic polymers
- Used materials to fabricate devices to demonstrate biological relevance
- Applied strategy to various substrate platforms

Acknowledgements

University of Michigan
Mark Meyerhoff
Robert Bartlett
Gail Annich
Terry Major
Dave Brant
Zhengrong Zhou

William Beaumont Research Institute
Charles Shanley
Michelle Johnston
Diane Studzinski

University of Kansas
George Wilson
Raeann Gifford