Design of Experiments Approach to Optimisation of a Biomaterial

R. O’Hara, F. Buchanan, J. Orr and Nicholas Dunne*
*Royal Academy of Engineering – The Leverhulme Trust Senior Research Fellow

School of Mechanical and Aerospace Engineering, Queen’s University of Belfast, UK.
Diseased or Damaged Bone

- Rheumatoid arthritis; 3 cases per 10k population per annum in US
- Osteoarthritis; 27m people in the US
- Osteoporosis; 1/3 women and 1/12 men +50yr of age worldwide
- Vertebral fractures worldwide ca. 1.4m, ca. 700k in USA (2009)
- Burst fractures account for ca. 15% of all spinal fractures*

* Denis, F., Spine (8), pp 817-831
Surgical Intervention

- Spinal Fusion
- Vertebroplasty
- Khyphoplasty

- PMMA based
- Composite based
- Calcium phosphate
Calcium Phosphate Cements

- CPC was developed in 1980, to be bioactive and stimulate bone formation
- Low temperature CPCs are made of precipitated HA, similar in composition to the mineral part of bone
- Two categories of CPCs exist: (1) apatite (PHA) and (2) brushite (DCPD)
- Problems include:
  - Poor mechanical properties
  - Limited to non-load bearing cases
  - Long setting times
  - Injectability issues

Comp strength: 10-50 MPa
Tensile strength: 1-10 MPa
Desirable Properties – Vertebroplasty

Clinical

Compressive Strength (MPa) 10-30*
Compressive Modulus (MPa) 50-800**

Injectable

Injectability (%) 100*
Initial Setting Time (Min.) 8*
Final Setting Time (Min.) 15*

**Bance, Sinc, Bailey, J Bone Miner Res 2006
*Jansen, J Orthop Clin N Am 2005

Vertebroplasty

Injectable

Resorbable

Final Setting Time

Biocompatibility

Mechanical Properties

Cellular Response
Research Aims

Manufacture and characterise CaP cements to meet surgical requirements

Stage One:
Determine the optimum cement parameters
Experimental Methodology

Input Factors & Parameters

- Weight percentage Na$_2$HPO$_4$
  - 1wt%
  - 5wt%

- Liquid to powder ratio (LPR)
  - 0.35mL/g
  - 0.50mL/g

- Type of HA
  - nano
  - micro

- Loading of HA
  - 0 wt%
  - 3 wt%

- Time in Ringer’s solution
  - 3days
  - 7days

**Design of Experiments**

- Optimum cement properties
- Factors affecting properties
- Interactions between factors
Experimental Methodology - Stage 1

DoE involved a two level factorial design using a $\frac{1}{2}$ fractional factorial

20 random experiments

Vs.

Full experimental study of 1

$\approx 120$ experiments
Experimental Methodology

**Compressive Properties:**
Specimens in Ringer’s solution (ISO 5833: 2002)

**Injectability:**
4g CPC, constant load applied to syringe of nozzle Ø 2.3mm

**Setting Times:**
Initial and final setting times using Gillmore Needle (ASTM C266)

Results: Compressive Strength

- Predominant factor influencing compressive properties was LPR. No strong interactions between factors studied and compressive properties. Overall contributions less ≤10% were deemed not to be significant.
Results: Injectability

- Factors influencing injectability were LPR and %wt Na$_2$HPO$_4$. Mild interaction between injection properties studied and LPR and %wt Na$_2$HPO$_4$. 

<table>
<thead>
<tr>
<th>Factor</th>
<th>Percentage Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Na$_2$HPO$_4$</td>
<td>14.01</td>
</tr>
<tr>
<td>LPR</td>
<td>64.50</td>
</tr>
<tr>
<td>Type of HA</td>
<td>0.08</td>
</tr>
<tr>
<td>Loading of HA</td>
<td>2.71</td>
</tr>
<tr>
<td>Time in Ringer’s Solution</td>
<td>0.01</td>
</tr>
<tr>
<td>Interactions</td>
<td>18.69</td>
</tr>
</tbody>
</table>
Results: Setting Times

- Factors influencing setting times were LPR and %wt Na$_2$HPO$_4$. No interaction demonstrated between LPR, %wt Na$_2$HPO$_4$ and setting properties of cement.
# Optimum Calcium Phosphate Cement

**Powder Component:** 100% α-TCP  
**Liquid Component:** 5 wt% Na$_2$HPO$_4$ at 0.35 mL/g  
**Testing Time:** 7 days in Ringer’s Solution

<table>
<thead>
<tr>
<th></th>
<th>Predicted</th>
<th>Actual</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compressive Strength</td>
<td>26 MPa</td>
<td>30.3 MPa</td>
<td>10-30 MPa</td>
</tr>
<tr>
<td>Compressive Modulus</td>
<td>1028 MPa</td>
<td>1010 MPa</td>
<td>50-800 MPa</td>
</tr>
<tr>
<td>Injectability</td>
<td>30%</td>
<td>52.6%</td>
<td>100%</td>
</tr>
<tr>
<td>Initial Setting Time</td>
<td>5 min</td>
<td>10 min</td>
<td>8 min</td>
</tr>
<tr>
<td>Final Setting Time</td>
<td>13 min</td>
<td>23 min</td>
<td>15 min</td>
</tr>
</tbody>
</table>

Acknowledgements

• Engineering Science Physical Research Council
• Queens University Belfast
• University Leeds
• Summit Medical Ltd.
• Smith & Nephew
• CMW Laboratories
• Klinipharm

• Dr Fraser Buchanan
• Dr Susan Clarke
• Professor John Orr
• Rochelle O’Hara
• Iwan Palmer

• Dr Ruth Wilcox
• Professor David Barton
• Sami Tarsuslugil
• Corinne Hanlon