

Structural Development and Optimisation of Sol-Gel Derived Bioactive Glasses

Overview and Context of Research Programme

The previously funded Kent-Warwick collaboration (through grants GR/L28647, GR/N64151/01 and GR/N64267/01) to understand silica-based sol-gel materials developed a powerful characterisation methodology combining a whole range of leading-edge techniques to include multinuclear solid state NMR, diffraction (neutron and X-ray), X-ray absorption (both Extended X-Ray Absorption Fine Structure Spectroscopy (EXAFS) and X-ray Absorption Near Edge Structure (XANES)), FTIR and UV-vis. Many of the technique advances that had been developed as a result of this previous programme were applied here to sol-gel prepared CaO-SiO₂ materials to give new insight into the structural features of the initial amorphous, precursors materials and their development with heat treatment, and then how this subsequently changes during bioactive reaction. Such calcium silicates are arousing much interest as bioactive scaffold materials that offer the genuine prospect of materials that will be used as surgical implants. This project extended the collaboration of the Kent-Warwick team to include Prof. Hench's group at Imperial. Prof. Hench's group brought the necessary expertise in the bioactivity of these calcium silicate materials, possessing extensive datasets of the bioactivity. Hence the atomic scale structural studies were carried out largely on exactly the same samples whose bioactivity had been measured. The presence of calcium in the samples meant that a whole new range of technique development was necessary including calcium XANES, ⁴³Ca MAS NMR and calcium isotope difference neutron diffraction. The philosophy of the project had two main aims – the development of novel atomic scale probes to provide new insight into these materials, and then apply these along with more conventional techniques to the formation of the initial amorphous calcium silicate materials, and then follow the structural changes on contact with simulated body fluid (SBF). The original proposal identified 5 specific scientific objectives (see form) and work was carried out on all. 1, 2 and 5 were completely achieved, with significant progress made on 3 and 4 (including collection of all the necessary experimental information to initiate molecular dynamics modelling and the commissioning of a cell for time-resolved/*in-situ* studies of the key elements of materials processing and behaviour). A number of the aspects of the work reported here were the first of their type in the literature, such as the detailed correlation of Ca XANES to structure, ⁴³Ca MAS NMR reporting such a range on nearest neighbour environments and the correlation to coordination number, ¹⁷O NMR to follow changes on dissolution in SBF and calcium isotope difference neutron diffraction to focus on the structural changes associated with the calcium.

Achievements of Scientific Programme: Summary of Outcomes

The main scientific highlights for this pair of projects were:

1. Developed calcium K-edge XANES as a probe of local coordination by reporting the most extensive set of such data from model crystalline compounds that can be used as a basis to identify unknown coordinations in more poorly defined (e.g. amorphous) compounds.
2. Reported the most extensive set of high field MAS NMR data from ⁴³Ca and revealed the effect of nearest neighbour coordination on the chemical shift for the first time, and determined the limitations of this approach for amorphous materials.
3. Applied the most comprehensive characterisation methodology to date (including multinuclear solid state NMR, synchrotron X-ray diffraction, Ca XAFS, FTIR, UV-vis and Raman) to follow the formation mechanism of amorphous calcium silicate monoliths.
4. Used calcium isotope difference neutron diffraction experiments for the first time to reveal directly and quantitatively the nature of the calcium bonding in sol-gel calcium silicate materials.
5. Used the comprehensive characterisation methodology (as in 3) to determine the structural changes on contact with SBF and demonstrate the key structural elements associated with bioactivity.

Detailed Description of Work Carried Out

1. Development of calcium K-edge XANES

The importance of calcium in a wide range of structural chemistry demands the development of sensitive probes of local structure. However there has been little previous systematic study of the calcium K-edge XANES and not enough information existed in the literature to ascertain how useful and sensitive this approach could be. This study rectified the situation by obtaining the most extensive such dataset to date.¹ It was found that a correlation exists between edge position and coordination number for coordinations below 9 (Fig. 1). For higher coordination numbers, the overall shape of the edge gives some indication of coordination. Hence, it is possible to use calcium K-edge XANES to determine the coordination number for Ca-O bonds up to 9 nearest neighbours where the shift of the edge position is 0.7±0.1 eV per atom. Hence combining the edge position

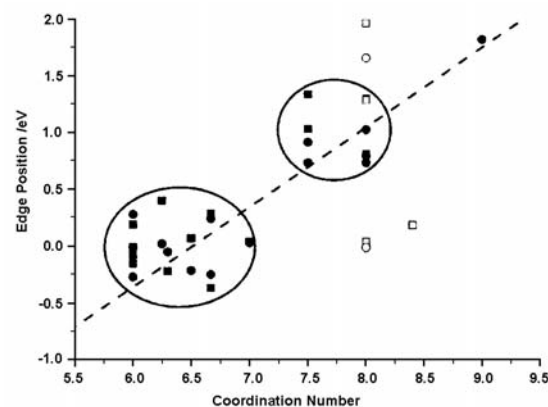


Figure 1. Correlation between Ca K-edge XANES position and coordination number.

with an analysis of the detailed shape will allow identification of the coordination in complex, amorphous materials with a high degree of confidence.¹

2. ⁴³Ca MAS NMR of inorganic materials

Solid-state ⁴³Ca NMR data are still scarce because of its low natural abundance (0.135%), small nuclear magnetic moment, and its possessing a quadrupole moment. Nearly all of the small number of solid-state ⁴³Ca NMR studies published to date have been on expensive enriched >50% ⁴³Ca. Only three previous natural-abundance ⁴³Ca solid-state reports existed and all of these involved materials with only Ca-O nearest neighbour bonds. In this study natural abundance ⁴³Ca MAS NMR data measured at a relatively high magnetic field of 14.1 T show that a good signal-to-noise ratio can be obtained from a large range of crystalline inorganic compounds.⁴ This is possible because generally calcium experiences a small quadrupole interaction, with the data collected here indicating that for inorganic ionic (or oxo salt) compounds, calcium sites have $\chi_Q \leq 4$ MHz. Thus the resonances narrow at 14.1 T at modest spinning speeds of < 4 kHz and so large diameter (e.g. 9.5 mm) rotors can be used. When oxygen is the nearest neighbour of calcium, the isotropic chemical shift is correlated with the mean Ca-O distance over a wide range of compounds, with the shift changing by ~ 280 ppm/Å. For the first time this study varied the nature of the nearest neighbour and a chemical shift range of ~ 250 ppm is observed. Some effects could be correlated with the electronegativity difference, but no general correlation could be found to include all binary compounds. Halogens gave very different trends compared to, for example, CaO and CaS. In sol-gel prepared calcium silicate materials ⁴³Ca MAS NMR spectra could be obtained for sol-gel samples heated at 120 and 350°C. However further heating causes the samples to become more disordered and no calcium signal could be observed. The data collected here strongly suggests that the broadening as the sample becomes more disordered is probably a result of much increased chemical shift dispersion and not an increased quadrupole interaction. The suggestion here is that even simple one pulse ⁴³Ca solid state NMR will be a very useful and sensitive probe of crystalline materials, but that other enhancement techniques and optimisation will be necessary for amorphous materials.

3. Structural development in the formation of bioactive calcium silicate materials

It is known from previous work at Imperial that the $(\text{CaO})_x(\text{SiO}_2)_{1-x}$ system displays bioactivity that varies strongly with x . The first task undertaken was to understand the structural evolution during the well developed production procedure of the Imperial group based on calcium nitrate and tetraethylorthosilicate (TEOS). Multinuclear solid-state NMR proved very effective at providing new insight into the structural development. The ¹⁷O NMR results reveal that at lower temperature (120°C), the network structure is dominated by bridging oxygens (Si-O-Si) with contributions from Si-OH. At higher temperatures (≥ 500 °C), metal cations begin to dominate the structural change of the silicate network by forming non-bridging oxygens (nbo). Two opposite trends of increasing (through hydroxyl loss) and decreasing (through interaction with calcium) polymerisation coexist at intermediate temperatures (~ 350 °C), where formation of nbo is still weak, which is very different from other mixed MO-SiO₂ (e.g. M = Ti, Zr, Nb, Ta) systems. The intensity of nbo resonance increases with increasing Ca/Si ratio in the materials, as well as with temperature. This is confirmed by ²⁹Si NMR data showing increasing Q² and Q³ resonances associated with increasing CaO content after heating at 500 °C. ⁴³Ca NMR results are consistent with ¹⁷O and ²⁹Si NMR data since in the gels at lower temperature the resonance more closely matches that of the starting nitrate material, and demonstrate ⁴³Ca as potentially an effective probe for some materials problems.⁸ However heating to temperatures where the nitrate breaks down the calcium signal becomes very broad. ¹⁷O solid-state NMR proved to be a very sensitive probe of bridging (bo) and non-bridging oxygen, with the MAS NMR spectra giving complete resolution of these species in this system. The changes in the bo:nbo ratio can be thus quickly and accurately followed in these materials by ¹⁷O NMR, and the equilibrium structure is not reached until above 500°C. To back up the detailed NMR study parallel work was carried using FTIR and FT micro-Raman that confirmed this picture of the reaction, and allowed their spectral features to be unequivocally associated with changes in the structure.⁸ X-ray absorption spectroscopy shows that there is no significant change in the coordination number of calcium as the sample composition changes.

4. Calcium neutron isotope difference experiments to examine the calcium site in bioactive silicates

Although a great deal of important information on the overall network structure was revealed by our more conventional X-ray and neutron diffraction experiments, there is a generic limitation in the sense that the all-important Ca-O 1st-neighbour correlation overlaps with the O-O correlation: it is therefore problematic to extract reliable information on the Ca-O feature alone. Neutron diffraction from samples with isotopic substitution (NDIS) allows extraction of information on both short and medium-range order in such glassy materials. No NDIS has been published on the subtle structural features associated with the novel modified amorphous calcium silicate networks generated by the sol-gel method. Two samples of $(\text{CaO})_{0.3}(\text{SiO}_2)_{0.7}$ were prepared, one isotopically enriched starting from ⁴⁴CaCO₃ (96 atom% enriched, Chemgas), this was converted to ⁴⁴Ca(NO₃)₂ by titration with 2M nitric acid, the resulting hygroscopic solid was dried at 130 °C until no further

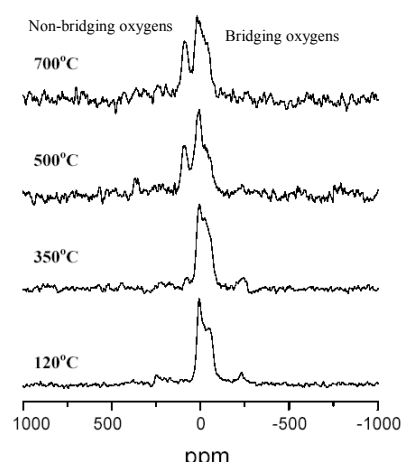


Figure 2. ¹⁷O MAS NMR spectra of sol-gel produced $(\text{CaO})_{0.3}(\text{SiO}_2)_{0.7}$

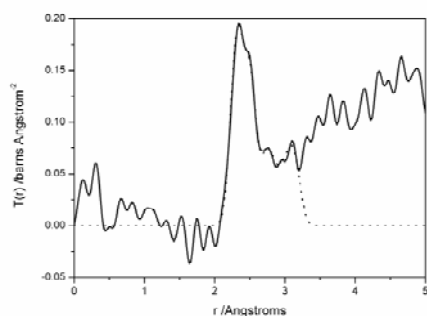


Figure 3. Difference correlation function, $t_{Ca-X}(r)$ for $(CaO)_{0.3}(SiO_2)_{0.7}$, obtained by FT of the difference between $i(Q)$ functions from the ^{44}Ca and ^{nat}Ca samples (solid line) and simulation of the $t_{Ca-X}(r)$ function (dotted line).

\AA^5 This is the first time a Ca-O environment of this complexity has been discerned in the context of contemporary bioactive glass materials: it is a key observation given the central role that Ca dissolution plays in the material's ability to promote bone growth. These NDIS results offer uniquely detailed quantitative data required for computer simulation studies of bioactive glasses, and in particular towards the full understanding of the Ca dissolution and subsequent mineral deposition processes. The data obtained point to the calcium being loosely bound at the surface of the silicate network, providing a direct atomic-scale explanation for the empirical observation that calcium loss from these materials is facile and can be achieved by simple ion exchange with SBF.

5. Reaction and structural alteration of calcium silicates on contact with SBF

EXAFS, XANES, X-ray fluorescence (XRF) spectroscopy and X-ray powder diffraction (XRD) have been used to study changes including the local calcium environment in these bioactive calcium silicate sol-gel glasses.^{2,3,6,7,9} The formation of a hydroxyapatite (HAp) layer on the composition with the highest bioactivity ($x = 0.7$) with time has been studied, in an *in vitro* environment, by immersion in SBF at 37 °C. The calcium-oxygen environment in all compositions studied was shown to be six coordinate in character. Both the EXAFS and XANES show a gradual increase in both coordination number and Ca-O bond distance with longer exposure to SBF. After the calcium sorption stage of the reaction with SBF, around 5 hours in solution, the coordination becomes closer to seven-fold; and after 30 days in an SBF solution, the calcium is in a fully seven-fold environment with Ca-O bond distances of 2.4 Å. XRF shows that calcium is quickly lost from the samples on exposure to SBF and the calcium concentration then recovers with time, and this is mirrored in the normalised magnitude of the calcium K-edge step (Fig. 4). There is clear evidence from XRD that the recovery of calcium content is due to the formation of an amorphous CaO-P₂O₅-rich layer. Amorphous calcium phosphate/HAp is present even after one hour

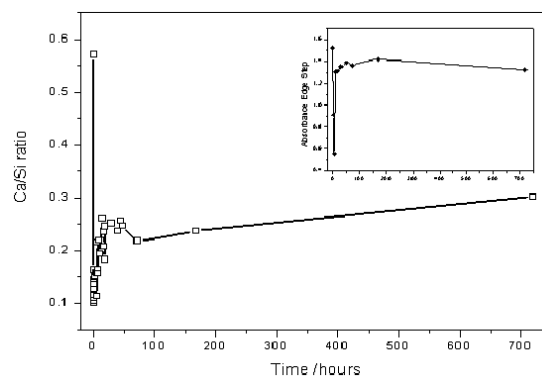


Figure 4. Variation of Ca/Si of $(CaO)_{0.3}(SiO_2)_{0.7}$ on exposure to SBF measured by XRF. Inset: Variation of EXAFS absorbance edge step with exposure to SBF.

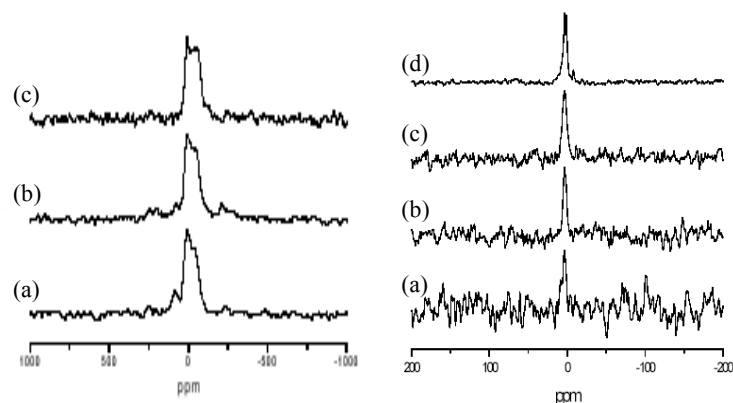


Figure 5. MAS NMR of S80 before and after SBF reaction ^{17}O (left) and ^{31}P (right) (a) before reaction, (b) 1 hour and (c) 24 hours, as well as (d) reaction of wollastonite with SBF for 1 day.

weight loss was observed. Hence the two samples showing contrasting neutron scattering from the calcium as the cross sections for coherent neutron scattering are $\sigma_{coh} = 278 \text{ fm}^2$ (natural abundance) and $\sigma_{coh} = 25 \text{ fm}^2$ (^{44}Ca). The NDIS experiment relies upon the samples being rigorously identical in composition and structure, so that the only difference is then the calcium neutron scattering: this was verified for our samples via X-ray diffraction, as well as He pycnometry (density) and X-ray fluorescence (chemical composition). The neutron diffraction spectra were collected on the GEM diffractometer at the ISIS spallation neutron source at the Rutherford Appleton Laboratory, which offers a world-leading Q-range and hence real space resolution.

The Fourier transform (FT) of the difference function, and the associated numerical fit are shown in Figure 3, and this provides information exclusively on the Ca-X pair correlations present in the material. The fit parameters obtained uniquely from the NDIS results show clearly that the Ca-O environment actually consists of distinct, but partially overlapping, correlation shells centred at 2.3 Å, 2.5 Å and 2.75

exposure to SBF solution, which becomes more crystalline on longer exposure. Annealing the samples at 650 °C allows this phosphate-based layer to recrystallise, thereby confirming its nature. Calcium EXAFS is consistent with the formation of an HAp layer. In XRD the first sharp diffraction feature changed shape strongly with the calcium content, so can also be used to follow the changes in the calcium content with exposure to SBF in a qualitative manner. On-going work is seeking to make the analysis of the calcium more quantitative.

Both FTIR and UV-vis are proving extremely effectively for *in situ* monitoring of structural changes of CaO-

SiO₂ materials reacting with SBF. With the detailed calibration provided by the other techniques these can now provide a rapid characterisation of the reaction with SBF.

Parallel multinuclear (¹H, ¹⁷O, ³¹P) solid-state NMR showed that the bioreactivity with respect to SBF reaction of sol-gel prepared calcium silicates depend strongly on the surface OH content, and that the presence of calcium aids HAp formation.⁹ ¹⁷O NMR shows the rapid loss of nbo (Fig. 5) as calcium is leached from the silicate resulting in a highly connected framework, and indicates the importance of achieving the right bo/nbo ratio for optimal biochemical and mechanical properties. ³¹P NMR confirmed formation of an HAp-like layer and suggests that it has quite a high degree of crystallinity. The nature of the silicate surface influences the nature of the phosphate phases formed.

Project Management, Summary of Expenditure and Progress of Research Programme

The PIs took responsibility for the parts of the project commensurate with their expertise. The Kent and Warwick PIs effectively taking the overall project management role. Regular contact on the progress of the research was maintained through full use of electronic communication so that when the situation warranted full involvement of the team in project discussions was ensured. The complete project team met for 8 minuted meetings during the 2 years, rotating around the 3 sites. The team also met frequently at the central facilities experiments. The expenditure and the use of central facilities on this project were as set out in the original case for support. All 3 centres coordinated their activity; the pdra staff at Kent and Warwick had start dates that closely matched. The PhD student at Imperial had to start somewhat later and was necessarily a 3 year project, but PDRA staff (see Personnel below) at Imperial were involved from the very start.

The programme of research largely proceeded as expected. All of the novel technique development was achieved as set out in the original case for support and because of the success of NDIS at providing new information on isotopically titanium-enriched sol-gel samples, the equivalent calcium experiment was pursued here. As envisaged extensive data from solid state NMR, X-ray absorption, diffraction (both X-ray and neutron), FTIR, UV-vis and Raman was collected. In the original case 5 specific scientific objectives were identified and work was carried out on all these, with three fully and two partially accomplished. One point to note is that this was the first 2-year project run by the PIs and although the time scale was appropriate for all the experimental work and analysis, the relatively short time nevertheless necessarily means that the number of submitted publications is lower than the work merits and will eventually achieve. A similar point pertains regarding the ability to secure the follow-up funding required to further facilitate some of the exciting discoveries made here.

Other Support and Further Research in this Area

The original applications had ticketed beamtime, but subsequent to the start of the grant the access arrangements to central facilities changed so that much of the time had to be bid for in normal direct access competition. All the beamtime needed to complete this project was awarded. In addition to that specified in the original application more access to X-rays was necessary and was bid for directly in peer review competition and successful bids related to these calcium silicate materials were made not only to the SRS, but also at the European centres E4 at Hasylab and IB15B at the ESRF. An EPSRC/ESRF studentship project (starting 10/02 Mr K.O. Drake, ref. CPG 299C6) entitled “Applications of synchrotron radiation to understanding sol-gel processing” was based around a range of the team’s sol-gel research. As part of this a cell has been designed that will carry out *in situ* and time resolved high energy X-ray diffraction from these samples; this has now been constructed and commissioned. The University of Kent also funded a studentship Ms L. Skipper through its Hyatt-Wolff fund and her thesis work entitled “A study of the atomic scale structure of bioactive sol-gel glasses” is directly related to this EPSRC project. The encouragement that this EPSRC project has given to the proposition that our methodology can provide real insight into porous bioactive glass calcium silicate scaffolds for tissue engineering applications has led to another application between the three sites. If funded this would (i) examine the effect of foaming on the texture and the local structure of gels, (ii) determine the effects of composition and processing on the network connectivity and silanol concentration, and the relation to bioactivity, (iii) determine changes in the calcium environment and the structure of the phosphate layer on contact with SBF, (iv) look at the effects on bioactivity of composition, processing and different precursor chemicals. It is only through the groundwork laid out here in GR/R57492/01 and GR/R59298/01 that such a proposal could be made.

The physical principles of the methodology have also nurtured new links, and a funding application with Prof. Knowle’s group at the Eastman Dental Institute has been made. This collaboration would look at phosphate-based glasses with potential as dental implant materials. The expertise developed in the group has brought two new aspects into this area of biomedical research: the application of the physical characterisation methodology used effectively to study the silica-based materials to the phosphate-based systems, and the novel use of the sol-gel approach to synthesise such materials, which has hitherto not been investigated. As a preliminary step to this an EPSRC-funded student has been working on these at Kent (Ms D. Carta) and funding of a Kent-Warwick-Eastman project in this area is currently being considered by the EPSRC. The next stage of planning the development and advanced characterisation of inorganic materials is already underway with apatite-based materials being considered for applications to the EPSRC and the EU. Also, although not directly funding work on these materials Johnson-Matthey currently have a CASE award at Warwick (02-05) on catalytic materials and will fund a new project on inorganic pigment materials commencing this October. It is the development work of solid state NMR techniques to characterise inorganic materials at Warwick that has encouraged this funding, and this development is only possible through such EPSRC funded projects. In a similar vein, Peter Layton and Associates (a

company focussed on the artistic and architectural use of glass) have approached the Kent team with a view to funding the development of a novel dichroic glass using sol-gel methods.

Personnel and Training

The pair of projects being reported here directly employed two PDRAs, Dr Sowrey at Kent and Dr Lin at Warwick. Although both had a formal chemistry training their synthetic chemistry skills were enhanced by the move into sol-gel materials which neither had worked on previously. Dr Sowrey coordinated much of the central facilities work, and took a lead in both the NDIS and Ca XANES experiments which were quite novel in their own right, meaning that Dr Sowrey had to learn new skills. Dr Sowrey also wrote a number of the beamtime applications associated with this work. Dr Lin also formed part of the team in many of the central facilities experiments giving him experience of new techniques. Dr Lin's main responsibility was the solid state NMR and he came with good training in the technique, this was mostly in conventional nuclei such as ^{29}Si and ^{27}Al . This project gave him experience of new nuclei especially ^{17}O , which meant he had to develop sample enrichment skills, and also in tackling a much more demanding nucleus ^{43}Ca . Both PDRAs and PhD students enhanced their presentation skill through reports at the regular quarterly meetings of the whole research team and made several conference presentations at both national and international meetings (1 talk and 11 posters). Both have developed skills that should make them attractive for physical science/materials technology employment, but both are at the stages in their career development where the lack of permanence of PDRA positions could influence their career paths.

Although not employed directly through these grants 4 other workers participated directly on this work on calcium silicates. There were two PDRAs at Imperial, Drs Saravanapavan and Jones. Jones has gone from a Lloyds Tercentary fellowship to a Royal Academy of Engineering/EPSC Advanced fellowship. The techniques learnt through participating in this project will form part of his fellowship project and he is a co-applicant on the EPSC proposal on calcium silicates currently being considered. Two students are also working on calcium silicates: Mr K.O. Drake as part of his project and Ms. L. Skipper, whose project is completely focussed on these materials.

Other workers benefited from the opportunities and facilities offered by these grants. A colleague Dr Mountjoy at Kent is supervising a DTA-funded student working on molecular dynamics (MD) modelling of calcium silicates. This has started off on crystalline calcium silicates, developed into melt-quenched glasses and will then focus on modelling the structures of sol-gel produced calcium silicate materials. It is the knowledge that the projects reported on herein have produced the highest quality structural data sets that is largely driving this. The EPSC student working on the phosphate system, Ms D. Carta, has benefited from the expertise made available by this project on sol-gel materials and techniques. Several final year undergraduate projects on related sol-gel materials were run in parallel using the facilities funded through these grants. Hence we believe we are able to demonstrate that this funding has given the opportunity for both "novice" and experienced research workers to further improve their skills a leading-edge research project in the materials field, allowed their development of generic skills, and has also fed into research-led undergraduate teaching.

Dissemination, Relevance to Beneficiaries and Collaboration

Four publications have already appeared or are in press in internationally leading journals. The nature of this work means that the publications have ranged from condensed matter physics (Phys. Rev. B) and Chemical Physics (Phys. Chem. Chem. Phys.), to those making contact to the most direct beneficiaries of this work (e.g. J. Biomaterials Research). One more has been submitted and at least 4 others are in preparation. One of the disadvantages we have learnt managing a project of only two years duration is that the time to get publications in press is much more limited. The project team believes that it was very active in disseminating the results from this project giving 13 talks, (7 invited) and 13 posters, many at meetings where the main beneficiaries of the research were present. It is pertinent to note that, having introduced the Imperial College Engineering group to the information that is accessible using our methodology, they were enthusiastic about joining the follow-up application currently under consideration by EPSC. This generic interest in the methodology for understanding biomaterials is further exemplified through the developing collaboration on sol-gel prepared dental materials with Prof. Knowles (Eastman Dental Institute). Longer term (5+) years the utility of the work carried out here may be judged by the citations that this work receives from others: not only from the group of direct beneficiaries, but via the possibility that this work should underpin wider research paths within tissue engineering in general. Tissue regeneration will reduce the need for transplants and donors so that surgeons, patients and health services may also benefit as the ultimate users of this research.

Appendix – Details of Publications and Presentations to which GR/R57492/01 and GR/R59298/01 contributed

Publications already published/submitted are numbered directly on the IGR form (1-5), papers in preparation and other forms of dissemination are presented here.

(a) Papers in preparation

6. *The regeneration of bone: an atomic-scale view of the reaction of calcia silica sol-gel glasses with simulated body fluid*, L.J. Skipper, F.E. Sowrey, D.M. Pickup, V. Fitzgerald, K.O. Drake, M.E. Smith, P. Saravanapavan, L.L. Hench, and R.J. Newport. Nature Materials.

7. *X-Ray Diffraction Studies of the Structure of Bioactive Calcia:Silica Sol-Gel Glasses As A Function Of Composition and of Reaction with Simulated Body Fluid* L.J. Skipper, F. E. Sowrey, D. M. Pickup, V. Fitzgerald, K.O. Drake, M.E. Smith, P. Saravanapavan, L.L. Hench, and R.J. Newport, J. Biomed. Materials.
8. *The structural evolution of sol-gel prepared bioactive amorphous $(CaO)_x(SiO_2)_{1-x}$ ($0.2 \leq x \leq 0.5$) studied by multinuclear solid state NMR, FTIR and Raman*, Z. Lin, F.E. Sowrey, L.J. Skipper, P. Saravanapavan, J.R. Jones, L.L. Hench, R.J. Newport and M.E. Smith, J. Mater. Chem.
9. *New insights into the dissolution mechanism of sol-gel prepared calcium silicate based biomaterials from multinuclear solid state NMR*, Z. Lin, F.E. Sowrey, L.J. Skipper, P. Saravanapavan, J.R. Jones, L.L. Hench, R.J. Newport and M.E. Smith, Interface.

(b) Invited Conference Presentations

10. *Detecting atomic scale ordering in glassy and crystalline materials by solid state NMR*, M.E. Smith, RSC Solid State Chemistry Group, Reading, 12/02
11. *Applications of solid state NMR to the study of technologically significant inorganic materials*, M.E. Smith, IUPAC Congress, Ottawa, Canada, 8/03
12. *The structure of sol-gel glasses*. R.J. Newport, National XAS SUG, Warwick, 5/04

(c) Invited Colloquia

13. *Applications of solid state NMR to understanding atomic scale structure of materials*, M.E. Smith, Department of Chemistry, University of Dundee, 02/03
14. *Applications of solid state NMR to understanding atomic scale structure of material*, M.E. Smith, Department of Chemistry, Nottingham Trent University, 03/03
15. *Applications of solid state NMR to understanding atomic scale structure of materials*, M.E. Smith, Department of Chemistry, University of St Andrews, 05/03
16. *The use of solid state NMR in characterisation of inorganic materials*, M.E. Smith, Department of Chemistry, University of Windsor, Canada, 05/04

(d) Contributed Conference Talks

17. *The atomic scale structure of sol gel materials*, R.J. Newport, UK-Ireland Sol Gel Meeting, Cranfield, 5/03
18. *Aspects of multinuclear solid state NMR as a probe of sol-gel produced materials*, M.E. Smith, UK-Ireland Sol Gel Meeting, Cranfield, 5/03
19. *Multinuclear NMR study of the structural evolution of amorphous $(CaO)_x(SiO_2)_{1-x}$ biomaterials*, M.E. Smith, RSC Solid State Chemistry Group, Loughborough, 12/03
20. *The use of neutron and X-ray scattering and solid state NMR as an advanced structural probes in the study of bioactive glasses*, F.E. Sowrey, D.M. Pickup, L.J. Skipper, D. Carta, K.O. Drake, M.E. Smith, P. Saravanapavan, L.L. Hench and R.J. Newport. 2nd Annual Biomaterials Conference, Cranfield, 03/04
21. *The structure of TiO_2-SiO_2 and $CaO-SiO_2$ sol-gel glasses from neutron diffraction and solid state NMR using isotopic enrichment of titanium, calcium and oxygen*, R.J. Newport, D.M. Pickup, F.E. Sowrey, L.J. Skipper, P. Gunawidjaja, K.O. Drake, M.E. Smith, P. Saravanapavan and L.L. Hench, NCM9, Corning NY, 07/04
22. *X-ray and neutron diffraction and solid state NMR studies of the growth of hydroxyapatite on bioactive calcia-silica sol-gel glasses*, L.J. Skipper, F.E. Sowrey, R.J. Newport, Z. Lin and M.E. Smith NCM9, Corning NY, 07/04

(e) Contributed Conference Posters

23. *Solid state NMR of ^{33}S and ^{43}Ca* , A.P. Howes, S.C. Kohn, Z. Lin and M.E. Smith, BRSG Easter Meeting, 04/03
24. *^{17}O , ^{29}Si and ^{43}Ca solid state NMR study of sol-gel prepared $CaSiO_3$ materials*, Z. Lin, M.E. Smith, F.E. Sowrey, R.J. Newport, P. Saravanapavan and L.L. Hench, UK-Ireland Sol-gel Group meeting, Cranfield, 05/03
25. *Structural studies of bioactive sol-gel glasses using X-ray techniques*, L.J. Skipper, F.E. Sowrey, D.M. Pickup, K.O. Drake, Z.H. Lin, M.E. Smith, P. Saravanapavan, L.L. Hench and R.J. Newport, UK-Ireland Sol-gel Group meeting, Cranfield, 05/03
26. *Sol-gel $CaSiO_3$ materials and calcium-containing inorganic compounds by natural abundance solid state ^{43}Ca NMR*, Z. Lin, M.E. Smith, F.E. Sowrey and R.J. Newport, Sol-gel 2003, Sydney, Australia, 08/03
27. *Multinuclear solid state NMR study of sol-gel prepared $CaSiO_3$ -materials*, Z. Lin, M.E. Smith, F.E. Sowrey and R.J. Newport, Sol-gel 2003, Sydney, Australia 08/03
28. *The atomic scale interaction of bioactive glasses with simulated body fluid*, L.J. Skipper, F.E. Sowrey, D.M. Pickup, K.O. Drake, Z.H. Lin, M.E. Smith, P. Saravanapavan, L.L. Hench and R.J. Newport, aphys 2003, Badajoz, Spain, 09/03, SET for Britain: Taking UK chemistry research and R&D to parliament in 2003, 11/03
29. *X-ray studies of the atomic structure of bioactive sol-gel calcium silicate glasses*, L.J. Skipper, F.E. Sowrey, D.M. Pickup, K.O. Drake, Z.H. Lin, M.E. Smith, P. Saravanapavan, L.L. Hench and R.J. Newport, Materials Congress 2004, London, 03/04, 2nd Annual Biomaterials Conference, Cranfield, 03/04 (i.e. presented at 3 separate meetings)
30. *Structural studies of bioactive sol-gel glasses using X-ray and NMR techniques*, F.E. Sowrey, L.J. Skipper, D.M. Pickup, K.O. Drake, Z.H. Lin, M.E. Smith, P. Saravanapavan, L.L. Hench and R.J. Newport, aphys 2003, Badajoz, Spain, 09/03, and 2nd Annual Biomaterials Conference, Cranfield, 03/04 (i.e. presented at 3 separate meetings)