Institution: Queen Mary University of London

Unit of Assessment: A3 (Allied Health Professions, Dentistry, Nursing and Pharmacy)

Title of case study: Apatite-based additives for oral care products

1. Summary of the impact

Researchers in the Dental Institute, working with Periproducts Ltd, have developed a toothpaste and mouthwash based on nano-hydroxyapatite that can treat dentine hypersensitivity and repair dental caries. It is marketed as UltraDEX® Recalcifying, and sold in Boots and major UK supermarkets. The researchers have also developed novel bioactive glasses for treating hypersensitivity. When they come into contact with saliva and water, these bioglasses release calcium, phosphate and fluoride ions, forming fluorapatite that binds to and protects the tooth surface. In 2012, Queen Mary signed an IP licensing agreement with a global healthcare company to commercialise the new glasses that form apatite faster than the bioglasses currently on the market. For a sense of the commercial potential of this development, the market for re-mineralizing hypersensitivity toothpastes is in excess of £6 billion per year.

2. Underpinning research

The underpinning research on apatites at Queen Mary's Dental Institute began with work by Professor Jim Elliott who wrote the classic book, "Structure and Chemistry of the Apatites and Other Calcium Orthophosphates", published in 1994. Elliott also invented X-ray microtomography, a technique that uses X-rays to create cross-sections of a 3D-object that can later be used to recreate a virtual model. In dentistry, this instrumentation is used to study small differences in the degree of mineralisation throughout dentine and enamel, which is of enormous value in the assessment of carious lesions. Since 2008, Graham Davis has further developed the technique and instrumentation of microtomography at Queen Mary. The unique availability of these advanced instruments provides opportunities for the research group to be involved in cutting edge dental research and has also opened up some interesting areas of interdisciplinary research in materials science, archaeology, palaeontology and petrology. For example, with EPSRC funding, Graham Davis has used the technology to read fragile historical scrolls that had been damaged to the point that they could not be physically opened. A fascinating project in itself, the technological benefits derived from this study of scrolls will further enhance the group's on-going dental research.

Following Professor Elliott's retirement, Professor Robert Hill and Dr Natalia Karpukhina joined Queen Mary in 2009, taking forward the Institute's apatite and glass research. The research team, now led by Professor Hill, has a world-leading understanding of bioactive glasses and apatites. In particular, Hill's team has developed the capability to perform accurate, reproducible fluoride-19 nuclear magnetic resonance spectra (19F NMR), an analytical technique used to identify fluorine-containing compounds that is widely used in dental research. 19F NMR is the only way that fluorapatite can be distinguished conclusively from hydroxyapatite. Fluoride plays a key role in preventing caries and promoting re-mineralization and therefore the ability to detect fluorapatite formation is of critical importance. The team has used 19F NMR to show the formation of fluorapatite with fluoride-containing bioactive glasses and to show remineralisation of enamel following application of toothpastes. Phosphorous-31 nuclear magnetic resonance has also been used to distinguish octacalcium phosphate (OCP) from hydroxyapatite. OCP is thought to be a precursor phase to hydroxyapatite in tooth and bone mineralization.

Prof Hill and Dr Karpukhina have worked closely with Dr David Gillam, an expert on dentine hypersensitivity who also has many years' experience in industry. The team also has the expertise on caries of Dr Paul Anderson and apatite crystallography skills of Dr Rory Wilson.

3. References to the research

Key publications:

1. **Davis GR Evershod ANZ and Mills D.** Quantitative high contrast X-ray Microtomography for Dental Research. Journal of Dentistry 2013; 41: 475-82.

2. **Mohammed, NR Kent NW**, **R. J. M. Lynch Karpukhina N, Hill R, and Anderson P**. Effects of Fluoride on in vitro Enamel Demineralization Analyzed by 19F MAS-NMR. Caries Research 2013; 47: 421-428.
3. **Brauer DS, Karpukhina N,** O'Donnell MD, Law RV**, Hill RG**. Fluoride-containing bioactive glasses: Effect of glass design and structure on degradation, pH and apatite formation in simulated body fluid. Acta Biomaterialia 2010; 6: 3275-82.
4. O'Donnell M, Watts S**, Hill R**, Law RV. The effect of phosphate content on the bioactivity of soda-lime-phosphosilicate glasses. Journal of Materials Science: Materials in Medicine 2009; 20: 1611-18.
5. **Brauer DS, Karpukhina N**, Law RV**, Hill RG**. Structure of fluoride-containing bioactive glasses. Journal of Materials Chemistry 2009; 19: 5629-36.
6. **Brauer DS, Karpukhina N**, O'Donnell MD, Law RV, **Hill RG**. Fluoride-containing bioactive glasses: Effect of glass design and structure on degradation, pH and apatite formation in simulated body fluid. Acta Biomaterialia 2010; 6: 3275-82
7. **Mneimne M, Hill RG, Bushby AJ, Brauer DS.** High phosphate content significantly increases apatite formation of fluoride-containing bioactive glasses. Acta Biomaterialia 2011; 7: 1827-34.
8. **Lynch E, Brauer DS, Karpukhina N, Gillam DG, Hill RG**. Multi-component bioactive glasses of varying fluoride content for treating dentin hypersensitivity. Dental Materials 2012; 28: 168-78.

Key grants

- MRC Grant No. G9824467.EPSRC (2001-2005) >£300k Elliott;
- EPSRC Grant EP/GOO7845/1 (2009-) "**High definition X-ray microtomography and advanced visualisation techniques for information recovery from unopenable historical documents**.**"** £786k Davis;
- BBSRC CASE Award New Remineralising Glasses for Toothpaste (GSK) (2010-2014) £130k Hill and Gillam;
- NMR Characterisation of Novamin® (GSK) (2012-2013) £40k Karpukhina and Hill;
- Numerous contracts with Periproducts Ltd of £9-16k (2010-2013) Hill and Gillam.

Research prizes

Professor Hill was awarded the Alan Wilson Memorial Prize for Dental Materials in 2013. Postgraduate students working on bioactive glass and related areas have won many awards (eg Mneime - 1st prize at 2010 GSK Research Day; Lynch – best student presentation at the 2011 GABA meeting in Switzerland; Ahmed – MINTIG Prize at 2012 BSDOR meeting, 2012 ORCA Young Scientist Prize for her research using 19F NMR to characterise fluoride uptake in enamel).

4. Details of the impact

4a. Overview

Apatite and bioactive glass researchers at Queen Mary have invented new dental materials for the treatment of dental caries and dentine hypersensitivity. Patents were filed and agreements established with commercial partners experienced in the oral healthcare market. The first products based on this research, a toothpaste and mouthwash based on nano-hydroxyapatite, are already being sold in Boots and major UK supermarkets under the brand name UltraDEX® Recalcifying. More recently, Queen Mary established an IP licensing agreement (subject to confidentiality restrictions) with a separate global healthcare company to commercialise one of the novel bioglass materials. For a sense of the commercial potential of these products, it should be noted that the market for re-mineralizing hypersensitivity toothpastes is in excess of £6 billion per year. Current products on the market include Colgate Palmolive's Sensitive Pro-Relief and GSK's Sensodyne, which became a 'billion-dollar brand' in 2012.

4b. Industry patents

Members of this research team are named inventors on four patents that have been filed and published during the REF period (see section 5a). The first two patents cover fluoride containing bioactive glasses. The third is a patent filed by Periproducts Ltd on the nano-hydroxyapatite toothpaste and mouthwash on which there are two Queen Mary inventors, Hill and Gillam. The fourth covers a bioactive glass composition for making a cement or an implant that has been invented by Hill, Karpukhina and Kent.

In March 2013, Prof Hill's team filed a GB patent (not yet published) on bioactive glasses and glass-ceramics containing chloride. This patent and the commercial plans to exploit it won the Armourers and Braziers Venture Prize, a national competition with a single £25k prize. The judging panel comprised three fellows of The Royal Society and leading Business Experts.

4c. Toothpaste on sale

Periproducts initially approached Prof Hill's team to test a prototype nano-hydroxyapatite toothpaste. This performed poorly with regard to remineralisation and dentine tubule occlusion. Subsequently Prof Hill and Dr Gillam worked with Periproducts and, using their knowledge and previously developed techniques for the characterisation of apatites, developed UltraDEX® Recalcifying toothpaste and mouthwash. An international patent (Patent 3 in section 5) has been filed by Periproducts on which Dr Gillam and Professor Hill are both listed as inventors. Queen Mary's contribution to the development of these products is also recognised on the product packaging [see 5b below]. The toothpaste is sold in the UK in 1,100 of the 1,300 Boots stores, as well as Waitrose, Sainbury's and Lloyds Pharmacy. It is also on sale worldwide via Amazon. The mouthwash is on sale in Boots and via Amazon. Both the mouthwash and toothpaste are based on a nano-hydroxyapatite, but they are marketed as 'biomimetic' products, to overcome any adverse views of nanotechnology in the target market of over 40 year olds.

4d. Fluoride-containing bioactive glass toothpaste being commercialised

The team has also developed fluoride-containing bioactive glasses and a patent has been filed for this technology (see section 5b, patent 2). In 2012, Queen Mary established a licensing option agreement with a global healthcare company to commercialise this technology. This agreement has already generated sufficient income (approximately £50k) to cover the costs of patent filing and the company recently embarked on a scaling-up process with a view to the commercial production of a fluoride containing bioactive glass on a greater than 1000kg scale.

The new glasses are being evaluated primarily for use in toothpastes to treat dentine hypersensitivity, which is estimated to affect 35 per cent of the world's population (Global Burden of Diseases study). In addition, the ability of these glasses to stick to the teeth and slowly deliver fluoride through a more effective delivery system also has potential to provide much better protection against caries whilst reducing the risk of dental fluorosis. By contrast, existing fluoride toothpastes use soluble sources of fluoride that are washed away by salivary flow. Consequently higher concentrations of fluoride have to be used. Recognized caries expert Ten Cate from ACTA in The Netherlands has said: "*For treatments to be effective longer than the brushing and salivary clearance fluoride needs to be deposited and slowly released."* (European Journal of Oral Science 1997; 105 (5 Pt 2): 461-5). In effect, this is what Queen Mary's researchers have achieved.

The novelty and commercial potential of the new bioactive glass toothpastes was recognised with the award of the Venture Prize. This major national prize led to extensive national and international press coverage, with two articles in the *Daily Mail*, as well as articles in dental trade (BDA) and professional journals (BDJ and ADA), and the engineering (The Engineer) and materials press (Materials World) [section 5c and 5d below].

5. Sources to corroborate the impact

5a. Published patents

- **Hill RG and O'Donnell M.** "Multicomponent Glasses for Use in Personal Care Products" WO 2011/000866A2 (Patent 1, January 2011)
- **Hill RG, Gillam DG, Bushby AJ, Brauer D, Karpukhina N and Mneimne MA.** "Bioactive Glass Composition" WO 2011/161422A1 (Patent 2, December 2011)
- **Hill RG,** Collings AJ, Baynes I **and Gillam DG.** "Multicomponent Oral Care Composition" Filed by Periproducts Ltd WO/2013/117913 (Patent 3, August 2013)

- **Hill RG, Karpukhina N and Kent N.** 'A Composition for Making a Cement or an Implant' WO2013093101 A1 (Patent 4, June 2013)
- **Hill RG, Karpukhina N** Chlorine-containing Silicate Glasses and Glass Ceramics (not yet published but won Armourers and Braziers Venture Prize)

5a. Pictures of commercial toothpaste and mouthwash

Note the labeling on the toothpaste 'developed by dental professionals'.

5c. National and international press

The research was widely covered in the professional and lay press (about 30 articles in total). Two examples below – from Daily Mail and Materials World.

Mini marbles that can repair decayed teeth

By ROGER DOBSON

TINY glass balls in toothpaste may halt decay and also help with sensitive teeth. The balls, which are no wider than a human hair, contain calcium and phosphate, crucial components of tooth enamel (the tough, protective outer layer of the tooth).

They have been developed to help repair teeth damaged by decay, but where the damage is not severe enough to warrant a filling.

As well as tackling decay, the glass balls may reduce the problem of sensitive teeth — where the tooth enamel is worn down, exposing the dentine, the softer layer underneath.

The balls, which have been created by a team of dentists and scientists from Queen Mary, University of London, are made from calcium phosphate glass.

Once the toothpaste containing them is brushed onto the teeth, the balls fill in areas of weakened or damaged enamel, or areas where the gum has started to come away from the tooth. The balls then start to dissolve in the moisture in the mouth, leaching out calcium and phosphate.

Early trials suggest that this forms a new surface on the teeth in less than three hours, with the balls dissolving completely in under eight hours. There are already several toothpastes made with glass particles on the market. However the team behind the calcium phosphate balls claim these dissolve eight times faster and form enamel more quickly.

They also say that the higher phosphate content means their glass balls repair teeth more effectively. The team have previously worked on a type of glass that contained fluoride to help strengthen teeth, but wanted to find a more effective way of actually repairing enamel.

The glass is of a special biodegradable type, known as bioglass, that has the ability to retain the calcium and phosphate when in a toothpaste, but releases them when in contact with lots of moisture — such as saliva in the mouth.

The technology recently won the team a £25,000 prize from the Worshipful Company of Armourers and Brasiers for innovation. The hope is to launch the product in the next two years.

Commenting on the technology, Hugh Devlin, professor of restorative dentistry at the University of Manchester, said: 'Bioactive glass materials in toothpaste is a "hot" research area.

'The trick is getting a product that can be produced in bulk commercially, as they take a great deal of expertise to manufacture.'

Picture: SHUTTERSTOCK

■ RESEARCHERS in Spain are investigating the use of biodegradable glass to heal broken bones.

Severe bone fractures can be hard to heal as the bone struggles to produce enough new cells to fill and repair the break.

The team from the University of the Basque Country say that a new bioglass could act as a type of polyfilla — it contains compounds such as growth factors that encourage new bone cells to grow and replace the damaged ones.

The treatment is currently in early stage trials.

MATERIALS WORLD

Fighting tooth decay with glass

Dissolving glass particles have been added to toothpaste to repair decaying teeth. Professor Robert Hill and Dr Pushkar Wadke, of Queen Mary, University of London, spoke to Eoin Redahan about their Venture Prize 2013 winning technology.

How exactly does the toothpaste work?

The toothpaste contains small particles that are matched to the size of the open tubules in dentine that cause tooth pain. They occlude or block the tubules, eliminating tooth pain. They can also remineralise incipient carious lesions that can result in tooth decay and tooth loss.

What degradable particles do you use?

The particles consist of a special glass with an open network structure that dissolves rapidly in saliva, releasing calcium and phosphate ions that then precipitate as an apatitic phase close to tooth mineral. The apatite-like phase forms a coating on the surface of the tooth that mimics the natural enamel layer.

How quickly does it repair teeth?

The glass particles dissolve rapidly and we can control this by changing the composition. The glass particle dissolution is pH dependant. In the laboratory, the glasses will form the apatite-like phase under neutral conditions in less than three hours. A single tooth brushing will be effective, but it is likely that regular use will increase the occlusion of the tubules and the thickness of the apatite layer, providing better long-term protection.

How are the degradable particles packaged?

Because the glass particles readily dissolve and react with water, the toothpaste formulation must not be water-based and is formulated with glycerol. In addition, a water-soluble polymer is added to provide the correct consistency. The polymer contains carboxylic acid groups that bind calcium ions in the glass and tooth and help keep the glass particles in place, stopping them being washed away by salivary flow before they convert to the apatitic phase.

"The apatite-like phase forms a coating on the surface of the tooth that mimics the natural enamel layer."

What were the biggest challenges?

Conventionally, we poured the molten glass into water – a process called fritting. However, some of the compositions we made were so surface reactive, and dissolved so fast, that we couldn't quench the glass into water and had to resort to other quenching methods.

When was the technology patented?

We have been working on the glass compositions for almost two years and we have filed a number of patents. However, the current patent was filed only recently.

How is your technology better than existing products on the market?

The glasses we have developed dissolve more quickly than those currently used in hypersensitivity toothpastes and form the apatite-like phase faster. The more open network structure results in them being softer. Consequently, they should abrade enamel away to a lesser extent during tooth brushing.

What is the next step towards commercialisation?

We hope to have a prototype in less than 12 months and have the toothpaste on the market within two years. Unlike medical devices, toothpastes are classified as cosmetics in Europe, which reduces some barriers to commercialisation.

The Armourers' and Brasiers' Materials Science Venture Prize aims to raise the profile of R&D. The £25,000 annual prize goes towards the commercialisation of promising research. For more information, visit www.armourershall.co.uk/materials-science

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5d. Press release

Press Release From Periproducts on UltraDEX Oral Rinse Detailing Collaboration with Queen Mary (ImpactUltraDEXpr): http://uk.prweb.com/releases/2013/9/prweb11112569.htm