Institution: University of Portsmouth

Unit of Assessment: 3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: The development and commercialisation of a polymer that reduces microbial colonisation on dental surfaces, thus improving oral health

1. Summary of the impact

A team of Portsmouth researchers has developed a transparent polymer coating that prevents colonising bacteria from adhering to the surfaces of teeth. In addition to protecting from decay, the polymer coating has the added benefits of reducing dental erosion, alleviating root hypersensitivity, and inhibiting the staining of teeth. GlaxoSmithKline (GSK) has adopted this technology and the polymer has been successfully developed into a component of "next-generation" oral healthcare products.

2. Underpinning research

The nature of the research insights or findings

Interactions between solid surfaces and microorganisms are of importance in areas such as biomaterials, biotechnology, clean-room techniques or the coatings industry. For example, materials for the biomedical device market (implants, valves, grafts, pacemakers, bone repair and replacement devices, artificial organs, dental materials, drug-delivery systems, separation systems, catheters and stents) accounts for annual sales of several billion US dollars. In another example, the protection of ships and submerged structures from marine biofouling is a major industry. Portsmouth researchers were the first to develop the "ultra-low surface energy" approach to the inhibition of bacterial colonization.[1,2]

Outline of what the underpinning research produced

The hypothesis underpinning the approach is based on the well-established Derjaguin-Landau-Verwey-Overbeek (DLVO) theory for the stability of colloidal dispersions: since in natural aqueous environments most surfaces and most bacteria (colloidal dispersions) are repelled by their respective negative charges, the utilisation of "ultra-low surface energy" coatings would minimize the competitive attractive (van der Waals) interactions operating between the target surface and the prospective coloniser, preventing the attachment of the bacterium onto that surface.

Key to the testing of the approach has been the molecular design[3] of fluoropolymers with time-independent surface energies of *ca* 6 mJ m^{-2} (the archetypal non-stick material polytetrafluoroethylene (PTFE, Teflon; surface energy *ca*. 18 mJ m^{-2}) is highly susceptible to colonisation by bacteria), and the development of pharmaceutically relevant methods for coating biological (teeth[4,5]) and other (glass, plastic, metal[6]) substrates. To this end, methods have been developed for the radical-induced, chain-growth synthesis of fluoropolymers in bulk, in solution, in suspension and, more importantly, in aqueous emulsion such that the fluoropolymers may be amenable to formulation in toothpastes, sprays, mouthwashes, gels, lozenges, chewing gums, tablets, pastilles, powders, oral strips and buccal patches.

Tested against a selection of bacteria and other fouling organisms, coated structures exhibited resistance to colonisation, validating the approach (see Figure 1).[1] *In vivo* (rat model) experiments, performed with reference to potential biomedical applications, confirmed the biocompatibility of the materials.[1]

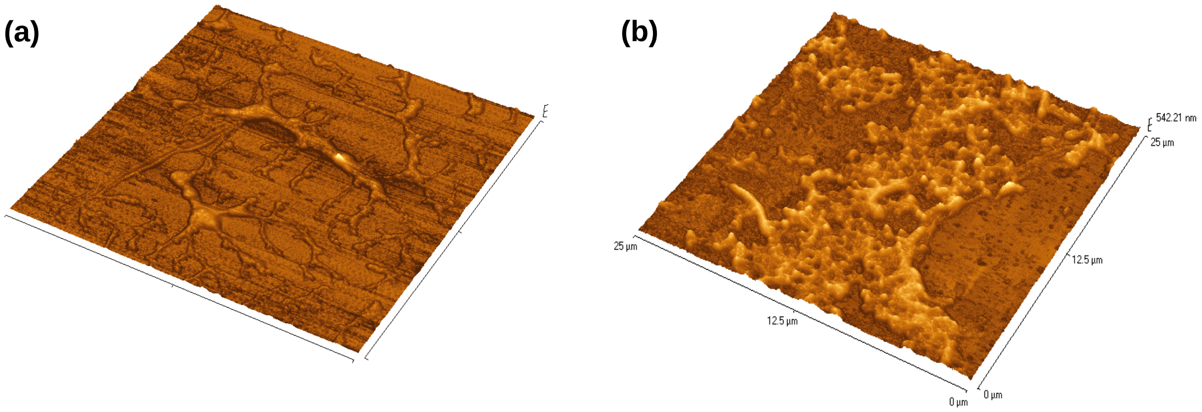

Figure 1. The Portsmouth fluoropolymer at work
Atomic Force Microscope (AFM) images of coated surfaces are shown after a two-week exposure to a bacterial culture (*Desulfovibrio alaskensis*). In **(a)**, the surface had been pre-treated with the fluoropolymer, poly (fluoroalkylacrylate). Bacterial colonies were seen to slide off this ultra-low energy surface as it was raised out of the culture broth. The surface in **(b)** had been pre-treated with a control polymer (PMMA). Bacterial colonies attached to this control surface could only be removed by physical abrasion.

Dates, names of key researchers and contextual information
This research project was initiated by Drs John Tsibouklis (Senior Lecturer 1994-1999; Reader 1999) and Thomas Nevell (Principal Lecturer; retired 2006) and received financial support from EPSRC and NERC (1994 – 1997, see also below). Following the publication of early scientific findings, industrial organisations, including GlaxoSmithKline (GSK) Dental Health, became interested in the exploitation of aspects of the technology.

3. References to the research

The underpinning research described above has been published in some of the top international journals in biomaterials and pharmaceutics. Funding for the research has been provided by UK research councils (BBSRC, EPSRC, NERC) and leading global pharmaceutical / healthcare industries (GSK and its predecessor, SKB).

1. **Tsibouklis J**, Stone M, Thorpe AA, Graham P, Peters V, Heerlien R, Smith JR, Green KL, Nevell TG (1999). *Preventing bacterial adhesion onto surfaces: the low-surface-energy approach.* **Biomaterials**, 20(13), 1229-123. DOI: 10.1016/S0142-9612(99)00023-X

2. **Tsibouklis J**, Graham P, Eaton PJ, Smith JR, Nevell TG, Smart JD, Ewen RJ. (2000) *Poly (perfluoroalkylmethacrylate) Film Structures: Surface Organisation Phenomena, Surface Energy Determinations and Force of Adhesion Measurements.* **Macromolecules**, 33(22), 8460-8465. DOI: 10.1016/S0032-3861(01)00777-7

3. **Tsibouklis J**, Nevell TG (2003) *Ultra-low surface energy polymers: the molecular design requirements.* **Advanced Materials**, 15(7-8), 647-650. DOI: 10.1002/adma.20030168
PDF copy can be supplied by the institution on request.

4. Churchley D, Rees GD, Barbu E, Nevell TG, **Tsibouklis J** (2008) *Fluoropolymers as low-surface-energy tooth coatings for oral care*. **International Journal of Pharmaceutics,** 2008, 352, 44-49. DOI: 10.1016/j.ijpharm.2007.10.024 Ref2 output: 3-JT-004

5. Nielsen BV, Nevell TG, Barbu E, Smith JR, Rees GD, **Tsibouklis J**, *Multifunctional poly(alkyl methacrylates)s films for dental care.* **Biomedical Materials** 2011, 6, 015003. DOI: 10.1088/1748-6041/6/1/015003

6. Mark A. McHugh, Alberto Garach-Domech, Il-Hyun Park, Paul Graham, Eugen Barbu, John Tsibouklis (2002), *Impact of fluorination and side-chain length on poly(methylpropenoxyalkyl siloxane) and poly(alkyl methacrylate) solubility in supercritical carbon dioxide* **Macromolecules**, 35(17), 6479-6482. DOI: 10.1021/ma012169i

External research funding to J. Tsibouklis and co-workers / UoP

BBSRC/SmithKlineBeecham. "Adherent oral coatings"; £46,000 awarded to J. Smart and J. Tsibouklis; 1998-2001.

EPSRC/GlaxoSmithKline. "Polymers for oral care products"; £58,500 awarded to J. Smart and J. Tsibouklis; 2001-2004.

BBSRC/GlaxoSmithKline. "Antimicrobial/polymer complexes"; £60,000 awarded to J. Tsibouklis; 2002-2005.

GlaxoSmithKline. "Multifunctional polymers for dental care", £70,450 awarded to J. Tsibouklis; 2004-2007.

GlaxoSmithKline. "Multifunctional films for dental care", £106,000 awarded to J. Tsibouklis; 2004-2007.

4. Details of the impact

In order to establish a colony on a surface, a microbe must first be able to adhere to that surface. Preventing such adherence is therefore a logical strategy for the prevention of microbial colonisation to the surfaces of biomedical implants, artificial organs and dental enamel, to name but a few. Microbial adhesion to teeth is a prerequisite to decay, so treatments that inhibit adhesion are prime candidates for inclusion in oral hygiene products. Furthermore, such dental coatings not only have the potential to reduce caries (cavity) formation, but also to limit the acid-induced demineralisation of enamel, the increased permeability of dentine (which leads to dental hypersensitivity), and the unsightly staining of tooth surfaces by, for example, spices, tannins and nicotine.

The Portsmouth team's innovative approach of using their ultra-low surface energy fluoropolymers to reduce bacterial colonization received considerable media attention (**ref.** 1). In turn, this triggered the attention of several industrial partners, each of whom signed evaluation licenses in the technology. These partners' application interests ranged from the inhibition of marine biofouling (DowCorning), through the prevention of soiling in engineering tools (Unilever), to uses in domestic household products (Reckitt Benckiser) and biomedical materials (GSK). *However, the greatest impact from the Portsmouth Team's research has been in the arena of oral healthcare through an ongoing collaboration with GSK* **(ref. 2**).

During the development of their fluoropolymer *as a dental care material, the Portsmouth team, in collaboration with GSK, found that (1)* the fluoropolymer coating, when deposited from aqueous emulsion, *greatly reduces demineralisation* of dental hard tissues by dietary acids, and the consequential tooth wear and erosion; (2) the fluoropolymer reduces dentine permeability as evaluated by the industry-standard hydraulic conductance model; (3) inhibits the adhesion to dental substrates of primary oral colonisers (*S. sanguinis, A. naeslundii*), a major aetiological pathogen implicated in dental caries (*S. mutans*), and a mixed bacterial culture isolated from human saliva; and (4) inhibits extrinsic staining by tooth chromogens such as the polyphenolic components of tea, coffee and red wine.

The obvious commercial potential of the Portsmouth team's fluoropolymer was immediately recognized by GSK who subsequently filed for patent protection of the intellectual property relating to the design of the fluoropolymer itself, to a process for its preparation, to oral care compositions comprising such polymers, and to its use in the prevention, inhibition and treatment of dental erosion, tooth wear, dentine hypersensitivity, anti-staining of dental enamel and anti-adhesion of oral bacteria.**(ref. 3)**

When added to toothpaste and/or mouthwash, such materials provide an efficient, biocompatible and cost-effective means of limiting the damage to teeth by oral bacteria. Therefore, the development of these innovative compounds as inhibitors of bacterial adhesion to dental surfaces has wide ranging benefits in **enhancing the oral health of the general public**, not only in the UK, but also worldwide. In the words of the Director of Gum Health and Dry Mouth Research and Development at GSK **(ref. 2)**, collaborations with the Portsmouth team "*have been very successful and have resulted in next generation products which have a big impact on the quality of life of patients and consumers.*" GSK toothpastes are sold world-wide and include many well-known brands in the UK, such as *Sensodyne®* *and Aquafresh®*.

5. Sources to corroborate the impact

1. Examples of the press coverage of the discovery of the ultra low-surface-energy approach as a non-toxic means for the inhibition of surface colonisation by bacteria;

1. **The Guardian**, 25/3/1999
   http://www.theguardian.com/technology/1999/mar/25/onlinesupplement1

2. **BBC Radio 4** (29/4/1999, 4.30 pm)

2. Letter

A letter from GSK acknowledging the contribution of the University of Portsmouth team to the development of next-generation oral healthcare products.

3. Patent

WO2007141330-A1, 13 Dec 2007. To: Eugen Barbu, David Churchley, Thomas G.Nevell, Gareth D. Rees and John Tsibouklis - assigned to **GSK**.

http://www.google.com/patents/WO2007141330A1

Patent that protects the invention that relates to a novel polymer, to a process for its preparation, to oral care compositions comprising such polymer and to its use in the prevention, inhibition and treatment of dental erosion, tooth wear, dentine hypersensitivity, anti-staining of dental enamel and anti-adhesion of oral bacteria