Polyhedral Oligomeric Silsesquioxane Nanocomposites: The Next Generation Material for Biomedical Applications

RUBEN Y. KANNAN,[†] HENRYK J. SALACINSKI,[†] PETER E. BUTLER,[‡] AND ALEXANDER M. SEIFALIAN*,[†]

Biomaterials & Tissue Engineering Centre (BTEC), University College London, London, United Kingdom, and Royal Free Hampstead NHS Trust Hospital, London, United Kingdom

ABSTRACT

The unique properties of nanocomposites have seen them creating the next revolution in materials science. Their quantal properties as a result of their size have given them unique physical characteristics, previously not possible because of classical physical laws. There is now evidence that these may also extend into the world of biology and medicine. In this Account, we look at the birth of a new generation of silica nanocomposites using polyhedral oligomeric silsesquioxanes, a promising nanoscale silica particle with particular use in cardiovascular interventional devices.

Introduction

Since time immemorial, materials have been the building blocks of civilization and have defined ancient history as in the Bronze Age, Iron Age, and Copper Age. In the last hundred years, man-made materials such as polymers have come into vogue. Today, millions of tons of these materials are used in our everyday lives. In addition, these materials have been reinforced with fillers at the micros-

cale level such as carbon fiber, graphite, and others to improve their mechanical properties. More recently, it has been recognized that their characteristics may be further improved by mixing them at the nanoscale level due to the quantum confinement effect,[1] lending support to the adage "Size does matter", by so doing obviating the laws of classical physics.

Nanocomposites

Definition. Nanocomposites are materials whose components are mixed at a nanometer scale. Due to their quantum-scale sizes, they can serve as bridges between molecules in the polymer. This nature allows them to exhibit different properties from conventional microcomposites.[2] Examples of this in nature are shells (Figure 1), bones, and teeth. Composite shells or nacre are composed of alternating calcium carbonate ($CaCO_3$) and nanoscale aragonite asperities[3] and, in so being, are 3000 times stronger than monolithic $CaCO_3$ crystals.[4] Man has since endeavored to synthesize nanocomposites, and it has been found that these synthetic nanocomposites have immense potential because they possess increased conductivity, mechanical strength, optical activity, and catalytic activity.[5] Their behavior is governed by the method of nanoreinforcement, the nano-interface, the synthetic process utilized, its microstructural effects, and the interaction between the polymeric and reinforcing component.[6]

Synthesis. Nanocomposites can be synthesized using the melt−intercalation, solvent method, or in situ polymerization method.[8] Whatever the method, the reaction generally involves hydrolysis and condensation. The final result depends on the phase separation during the catalyzed sol−gel process. The ultramorphology of these nanocomposites depends on the rate of hydrolysis or condensation as well as the sol−gel catalyst. Faster hydrolysis predisposes to simple or branched silica matrixes, while filament-like nanostructures are formed as a result of rapid condensation. Sol−gel catalysts also affect the physical properties of the nanocomposite.[9] While acid-catalyzed processes form dismal nanocomposites, base-catalyzed reactions cause villae formation on their surfaces because only the hydrophilic components of the polymer absorb water and expand and not the inorganic constituents, which form a rigid network. On the other hand, when

Ruben Kannan, after completing his basic medical degree at the Christian Medical College, Vellore, India, from 1993 to 1999, went on to do his basic surgical training under the Royal College of Surgeons of Edinburgh from 1999 to 2001, obtaining his membership exams in 2001. Then he followed on plastic surgery training at the University Hospitals of Birmingham. Currently, he is in the final year of his Ph.D. work at University College London, working on nanocomposite polymers for development of microvascular networks as building blocks of an artificial capillary bed, devices that would make artificial organ transplantation a distinct possibility. His research interest is on nanomaterial technology including plastic surgery applications.

Henryk Julian Salacinski is a chemist and obtained his B.Sc., M.Sc. and Ph.D. from University of London. He was appointed postdoctoral fellow at University College London in 1998. He has worked there since and his research interests include nanocomposites and tissue engineering for development of medical devices.

Peter Butler is a graduate of the Royal College of Surgeons and Physicians of Ireland and obtained his medical degree in 1987. After general surgical training, he obtained Fellow of the Royal College of Surgeons in Ireland and England. He began training in Plastic Surgery in Dublin followed by a research fellowship at the Massachusetts General Hospital and Harvard Medical School, Boston, MA. He obtained his M.D. in the USA. Currently he is a consultant Plastic Surgeon at Royal Free Hampstead NHS Trust Hospital. He is actively collaborating with the tissue engineering group at Harvard Medical School, Boston, and held a Hon Consultant in Plastic Surgery at the Massachusetts General Hospital, Boston.

* Corresponding author. Tel: ++ 44 20 7830 2901 (direct). Fax: ++ 44 20 7472 6444. E-mail: A.Seifalian@UCL.AC.UK.
† University College London.
‡ Royal Free Hampstead NHS Trust Hospital.

Alexander Seifalian received a degree in Nuclear Physics from the University of London in 1982, followed by Master and Ph.D. degrees from University of London. Currently, he is Professor of Biophysics and Tissue Engineering at University College London. His current interest is development of medical devices, including bypass graft, stent, heart valve, and cartilage using nanocomposite polymers and tissue engineering. He has developed several products from laboratory to commercialization, including a dialysis access bypass graft, which obtained CE mark and FDA approval and is currently commercialized. He is editor of several journals and has over 200 peer-reviewed publications. He is Fellow of Nanotechnology and Institute of Physics.
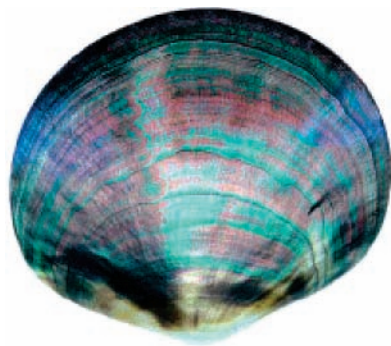
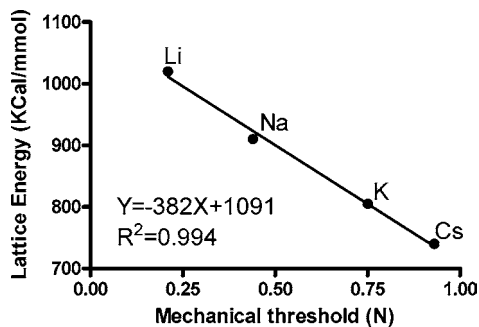**FIGURE 1.** Sea shells—a prime example of a biological nanocomposite.[7]

FIGURE 2. The effect of catalytic cation type on nanocomposite strength, adapted from ref 10.

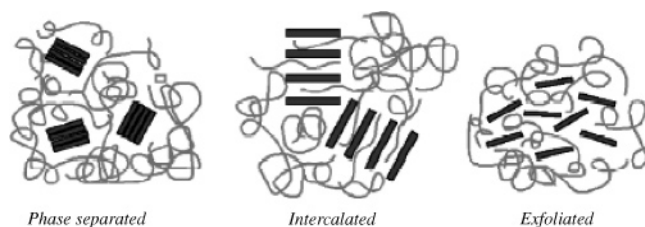*Phase separated*   *Intercalated*   *Exfoliated*

FIGURE 3. Types of synthesized nanocomposites. Reprinted with permission from ref 11. Copyright 1999 Springer.

nanocomposite formation is catalyzed with salts (anionic reaction) during condensation, material strength may be increased by weakening the bond between the anionic and cationic component of the salt as illustrated by Figure 2. In other words, weaker salts improve interfacial interactions between the inorganic (ceramic) component and the organic constituents thus conferring improved elasticity and flexibility to the nanocomposite.[10]

Structure. Conventionally when the components of a composite are mixed, phase separation occurs resulting in the formation of microcomposites. In nanocomposites however, the nanofillers are able to intercalate between the layers of the matrix (intercalated type) or be even further dispersed uniformly within the matrix to form exfoliated nanocomposites thus maximizing the surface area for component interaction. While intercalated nanocomposites have regular interlayers, exfoliated ones have larger interlayers (Figure 3).

Classification. Once formed, nanocomposites exist as stacked layers separated by an interface termed "interlayer" or "gallery". The anionic nanofillers such as clay

confer negative charges to each layer, which can be counterbalanced by the addition of exchangeable cations at the interlayer. The surface energy of these nanocomposites may hence be manipulated by altering the ionic composition of these adjacent layers.

Depending on the ultrastructure of the synthesized nanocomposite, Novak in 1993 classified nanocomposites as being of the following types:[12]

I. Organic polymer embedded in an inorganic matrix without covalent bonding between the components.

II. Organic polymer embedded in an inorganic matrix with sites of covalent bonding between the components.

III. Coformed interpenetrating networks of inorganic and organic polymers without covalent bonds between phases.

IV. Coformed interpenetrating networks of inorganic and organic polymers with covalent bonds between phases.

V. Nonshrinking simultaneous polymerization of inorganic and organic polymers.

The commonest types synthesized are types I, II, and V.[12] Type I composites form an inorganic, completely interpenetrating network around an organic polymer component with no covalent bonding. Greater interpenetration between its components results in stronger, more resilient, and optically transparent materials. When there exists covalent bonding between the organic and inorganic components of the nanocomposite, these materials are classified as type II nanocomposites. A prime example of this would be silane molecules with reactive pendant groups such as isocyanates bonding covalently with the organic component. When the organic and inorganic components are polymerized together, it prevents the loss of the solvent during hydrolysis for it is solvent loss that causes material shrinkage and cracking as a result of capillary pressures. These novel nanocomposites have been classified as type V. When the interpenetrating network is composed of both inorganic and organic phases, it is classified as type III or IV depending on the presence of covalent bonding.[9]

Due to the size of these nanofillers, their surface areas are up to 400% more than conventional microfilled composites. These are advantageous because their mechanical strength, optical properties etc. are accentuated. Therefore nanofiller dispersion is crucial during synthesis either by direct blending or by in situ polymerization. Dispersion is dependent upon the shear force between particle and the polymer. This may be further increased by making these nanofillers compatible with the remaining polymer. Alternatively, these nanofillers may be directly polymerized.[13]

Characteristics. A unique property of nanocomposites is nonlinearity. *Z*-scanning of these nanocomposites has shown high degrees of nonlinearity. This has been attributed to the "free carrier" effect.[14] This effect, normally seen in semiconductors, is due to the difference between the electron acceptors and donors within the material.[15] The dielectric property of nanocomposites is due to the presence of Stern−Gouy−Chapman layers acting as in-
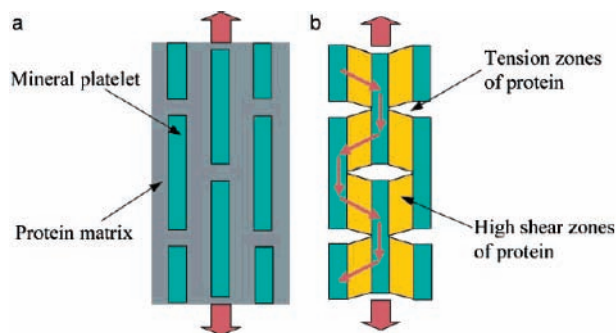
FIGURE 4. Schematic representation of the interfacial effects of nanocomposites when subjected to mechanical loading. Reprinted with permission from ref 4. Copyright 2003 National Academy of Sciences.

teraction zones around the particles, which form quasi-conducting paths within the composite.[16] Others have attributed the direct current ionic conductivity of nano-composites to be due to the variable range-hopping mechanism whereby its alternating current conductivity arises from the small polaron tunneling mechanism.[17] This results in the presence of unstable surface free energy as well as the ability to conduct electrical impulses.

As discussed earlier, nanocomposites have far greater mechanical strengths[18] than their constituents. Studies have shown that their strength is based on the arrangement of nanofillers or "mineral platelets" within a soft protein matrix as shown in Figure 4. While the nanofillers confer tensile strength to the composite, the interfacial shear attributable to the lubricating proteins allows for efficient load transfer due to the significantly enhanced surface area/volume ratio of the composite.[19] The Griffin criterion states that in composites with fillers below a critical length, the strength of the composite, even if cracked, is virtually equivalent to a solid crystal. This holds true for nanocomposites and explains the relative immunity of nanocomposites to fracture.[4]

Conventionally, increasing filler content within size-selective polymers decreases the polymers' permeability in accordance with the Maxwell equation. Transport through these polymers normally depends on their free volume content wherein larger spaces allow greater permeability. These voids may be classified as static or dynamic. The former depends on polymer packaging, while the latter is a temporary[20] effect due to thermally induced polymer chain rearrangement. On the other hand, nano-composites exhibit a phenomenon called "reverse-selectivity".[5] This has been hypothesized to be due to nano-fillers, which prevent close packaging of the polymer by augmenting void space within the polymer without increasing free phase flow through the nanomaterial. In simple terms, reverse-selective nanocomposites preferentially allow larger molecule transport through the composite than those of smaller sizes. This phenomenon could, in particular, have far ranging implications in biological membranes.[5] More recently, studies have begun to show that these nanomaterials have the ability to distort the conformation of adsorbed proteins thereby inactivating them.[21]

When semiconductors have band gap energies of 3 eV or less, which lie within the visible light band region, they can convert solar energy into chemical energy. This characteristic is inversely proportional to the semiconductor's constituent particle sizes.[22] Nanoengineered materials such as sub-nanometer CdS and TiO_2 particles have been shown to possess greater photocatalytic effects than conventional photocatalytic semiconductors.[23] Photocatalysts such as TiO_2 nanocomposites are exposed to light; they release highly reactive hydroxyl radicals in a redox reaction induced by light, which has been shown to inactivate bacterial endospores.[24] This property would make these nanomaterials ideal for resisting infections.

Current Nanocomposites. Nanocomposites may be either biological,[3] synthetic, or hybrid.[26] The current types of synthetic nanocomposites may be broadly classed into clay-, carbon-, metal-, or glass-reinforced nanomaterials.[27] The most common nanofillers used seem to be silicon-based ones. Clay-based nanocomposites are usually layered in the form of montmorillonite, hectorite, or saponite,[11] while metal oxides such as ZnO and TiO_2 have also served as nanofillers.[28] Carbon-based nanocomposites[29] exists as single or multiple nanotubes.[30,31] These can be grown in vitro as crystals. More recently, even silicon heterostructures have been grown.[32]

Nanocomposites are amphiphilic, thermodynamically stable, biodegradable, and biocompatible with good distribution within biological systems.[33] This, along with their small size ($\sim$20 nm) and surface characteristics, slows reticulo-endothelial system degradation making them ideal as nanocarriers. In vitro studies on anionic nanocarriers of low-density lipoproteins (LDL) have so far been encouraging.[34] Their unique properties have also seen them being used in a variety of biomedical devices such as nanowires[35] or microelectrodes.[36] In the second half of this Account, we shall dwell on a novel type of silica nanofillers called polyhedral oligomeric silsesquioxanes (POSS) and their derivatives.

Polyhedral Oligomeric Silsesquioxanes

In contrast to siloxane, silsesquioxanes (SQS) exist as ladder- or cage-type nanostructures.[37] These three-dimensional organosilicon oligomers are formed by complete hydrolytic condensation of their trifunctional monomers, Si_4O_6 (see Figure 5a). The strong intermolecular forces between their constituent molecules and neighbors, as well as their strong framework with their shorter bond lengths (Table 1) make these silica nanocomposites even more resistant to degradation.[38]

In 1995, Lichtenhan and co-workers[39] developed and patented a closed-cage SQS, POSS or molecular silica,[40] as shown in Figure 5b. These molecules are composed of two cyclic rings of oxygen and silicon in accordance with the stoichiometric formula $(SiO_{1.5})_n$ where n can represent 8, 10, or 12 repeats (Figure 5a). The POSS molecule is in the octameric form with well-defined nanoclusters having an inorganic silica-like core surrounded by eight organic
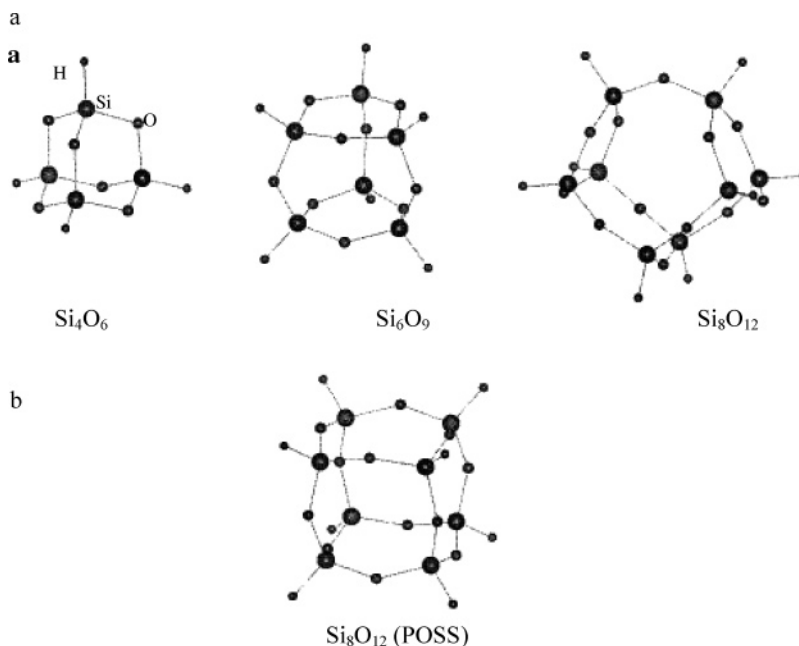
FIGURE 5. Molecular structures of (a) silsesquioxane $(SiO_{1.5})_n$ molecules with 4, 6, and 8 repeats where Si_4O_6 represents the monomeric component of POSS molecules (please note that the molecular formula Si_8O_{12} can exist in the non-POSS form as shown in the far right image) and (b) the cubic POSS molecule with its constituent molecules spread out in a symmetric fashion.[25]

Table 1. Bond Lengths and Bond Angles between the Molecules in a POSS Nanocage

molecules	bond length (nm)	molecules	bond angle (deg)
Si–H	0.147	O–Si–O	110
Si–O	0.170	Si–O–Si	137–148
Si–Si	0.540		
Si–C	0.230		

corner groups, which can be replaced by X–X′ functional groups to form homosilsesquioxanes,[38,41] or to be formed into dendrimers or used as nanobridges.[42–44] Depending on the number of side groups, they may exist as pendant cages, be part of a polymeric backbone, or be cross-linked. Researchers have since shown that these nanocomposite cubes may be incorporated as building blocks[45] of controllable shapes[43] into other polymers to form hybrid inorganic–organic copolymers[46] with improved miscibility and elasticity.[47]

Continuous-space Monte Carlo simulations on POSS network structures have shown that increasing linker length while reducing the reactiveness of their tethers increases the intercubic pore sizes within the nanocomposite thus resulting in an even distribution of the nanocages. This prevents the formation of large mesopore and bulk cavities. However, this effect is countered if their tethers are rigid because the degree of cross-linking would be reduced.[48] Studies have shown that POSS nanofillers increase the glass transition temperatures (T_g) at higher concentrations by reducing the distances between these nanofillers, thereby aggregating them. This effect hinders molecular or segment rotation with reference to the polymer and reduces its dipole interaction potential, thus making the polymer stronger.[49]

In the world of cardiovascular interfaces, a much sought after goal is the duality of amphilicity and anti-thrombogenicity.[50–52] While anti-thrombogenicity prevents

early graft occlusion, amphilicity of its surface would ensure optimal endothelialization. There have been reports that POSS acts as an amphiphile at the water–air interface,[53] a characteristic that has already prompted researchers to patent these for use at the vascular interface such as stents.[54,55] We have synthesized a novel type II nanocomposite, single functional side-group POSS molecules in the form of a pendant side chain attached to poly(carbonate–urea)urethane (PCU),[56–58] similar to that synthesized by Fu and colleagues.[59] We utilized the octameric POSS molecule because studies have shown that nonlinearity and dielectricity is better when the number of repeats (n) is 8 or less.[60] By combining polymer science and tissue engineering, we intend to create the building blocks of an artificial capillary bed,[61] and studies to this effect are currently being carried out.

We have shown that POSS nanocomposites, unlike carbon nanotubes,[62] are cytocompatible and hence suitable for tissue engineering. We have shown that there was no significant difference in cell viability, adhesion, and proliferation between POSS nanocomposites and standard cell culture plates.[63,64] Further experiments are now afoot to assess their thrombogenic potential, hypothesized to be due to reduced adsorption of proteins and platelets responsible for activating coagulation. Our postulate is that a pendant nanocage containing silicon atoms would form foci of silicon-rich areas with increased surface free energy thus allowing endothelialization and repelling coagulant proteins.[65] In addition, the inorganic POSS matrix confers a viscoelastic effect to the bulk of the nanocomposite,[66] which is useful in vascular prostheses.[67] In summary, the combination of the unique POSS molecules and polymers holds great promise for the future of biomedical devices, especially at cardiovascular interfaces.

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