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Nanoengineering Approaches to Design Advanced Dental Materials for Clinical Applications

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The development of dental materials for clinical applications is largely based on complex physico-chemical approaches involving traditional energy intensive and chemical routes. However, there is growing attention towards designing new recipes which can shift dental material design from bio-inert to bioactive in order to regulate the biological response of biomineralized tissue. This article reviews current nano-engineering approaches and applications to design nanomaterials for advance clinical applications in dentistry, considering physical properties, aesthetics, surface texture and hierarchical assembly of tooth anatomy. In addition, this article gives an overview about the benefit of micro-nanoscale material design over conventional dental material arising due to advance nanoscale material properties. Biomimetic nano-engineering route via top-down and bottom-up approaches and subsequent opportunities/challenges aiming to future applications are discussed.

Keywords:

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1. INTRODUCTION

If one would ask which the most promising fields are for materials scientist in biomedicine; the answer should be the orthopedics and dentistry. However, surfing the search engines to find the cross collaboration between the material sciences and clinical dentistry practice, most of the data has been published from research institutes rather than hospital clinics, albeit more contribution is expected for successful biomedical applications between the two fields. Thus, there is growing need to engage practicing dentists in practice based dental material research to establish more cross talk between material sciences and clinicians.[1]

In recent decades, application of materials at bio/micro-nanoscale in biomedicine, have received greater attention due to availability of superior synthesis recipes and characterization protocols with novel applications.[2] The intense interests for nanomaterial application in dentistry arise due to the fact that material properties (electrical, chemical, mechanical and optical) at nanosclae can be smoothly controlled by their synthesis protocols.[3] There is rapid proliferation of published articles in dentistry containing the term "nano" with special reference to nanoscale characterization (morphological, physical) and restorative recipe containing nanoscale features. However, there is substantial scarcity of information detailing the approaches to design nanoscale materials for dental applications.[4] Here, we review the nanoscale approaches and applications to design the materials for advance dental application.

2. REQUISITE OF FUNDAMENTAL DESIGN PROPERTIES FOR DENTAL MATERIAL APPLICATION

Considering the properties of dental materials at micro-nano interface, following are the main requisites to be considered in design features.

2.1. Physical Properties

The materials must compensate the routine masticatory forces without fatigue and wear/tear loss. In addition,

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physical properties of new materials should genuinely exhibit thermo-physico-chemical resistance towards thermal changes; wear like attrition, abrasion and resistance to unwanted chemical erosion due to changes in pH in oral environment. Moreover, the ability to fuse and making bonds with natural tissue in oral cavity should be one of the most important characteristics to new materials for dental application.[5]

2.2. Biocompatibility

Biocompatibility defines how well the new materials coexist with the biological equilibrium of the natural tissues in the oral cavity. Thus, the most important characteristic of material design for dental restoration and implant application is biocompatibility issue. Since we need to integrate synthetic materials in close contact with mucosa, tooth, and pulp, ascertainment of non-toxic state must be considered in synthetic recipes. The demerits of current dental materials like allergies, chemical leakage, and pulpal irritation thus could be avoided by designing biomaterials under soft biological conditions, adopting biomimetic approaches.[6] Current approaches in materials sciences harbors vast molecular and physical information in creating extracellular influences on materials by coupling biocompatible short functional domains, to recreate fillers, implants materials and restorative cements for dentistry. This is termed as bottom-up approach in materials science.

3. CONVENTIONAL DENTAL MATERIALS IN PRACTICE

3.1. Bonding System

In early 50s, dentistry started with no bonding system. Later system shifted to enamel bonding, dentine bonding and now combined enamel/dentin bonding systems is in fashion in clinics.[7] Advance in dental material sciences has introduced bonding system in many shades and flavors after passing through many generations of evolution. The classification scheme of dentin bonding systems is broadly based on its ability to make bond with dentin considering the number of components utilized, their actions, and/or the type of acid being used.[8] Conventional three-component systems comprise etching (E), priming (P), and bonding (B) operations.[9] Etching is prerequisite before priming and bonding to remove the smear layer and decalcify intertubular zones of dentin. Etchants (generally inorganic acids; phosphoric acids) must be quick and strong to assure the decalcification process in few seconds and then primers are applied immediately to enhance wettability and flow on the substrate to optimize the surface characteristics of the dentin. In the final step, a bonding agent comes in picture to chemically bridge between the hydrophilic primer and restorative material. To enhance the efficacy, multiple (n) priming step are recommended, thus representing bonding system as $E + nP + B$.[9] Subsequent developments have taken place in response to practitioner's agitation to reduce the steps due to complexity of procedure. In early 90s Japanese dentists introduced acidic monomers to combine the etching and priming steps i.e., three step system shrunk to nEP + B while American practitioners were more keen to retain the Etching system, combining the Priming and boding system i.e., E + nPB. The latter gives advantages of fast and reliable bonding since etching step assures removal the smear layer and decalcification of intertubular zone.[10]

Further evolution of bonding chemistry combined all three functions into a single package (nEPB), producing one-component systems called self-etching adhesives. Here, adhesive, initiator, and applicator compartments are available in three pouches (Adper™ Prompt™ L-Pop™), ready to mix the two components and load the applicator at chairside.[11]

New materials design technologies at micro-nanointerface have advanced the dental bonding system and currently all-in-one adhesive system are available which give "Super Dentine" formation upon bonding as shown by microscopic analysis of nanostructure of acid-base resistant zone (ABRZ) at the adhesive/dentin interface.[12] Introduction of ABRZ by all-in-one adhesive at the underlying dentin reinforces normal dentin against dental caries, giving it status of super dentin. Moreover, advances in nanotechnology had given another approach to improve the performance of bonding system beyond its composing steps. Application of Colloidal Platinum Nanoparticles (CPN) before the application of 4-META/MMA-TBB (4-methacryloxyethyl trimellitate anhydride/methyl methacrylate-tri-n-butylborane) resin cement, prolonged the durability of bonding system by inhibiting the routinely secreted catastrophic enzymes in oral cavity which are suggested to catalyze the decomposition of resin composites of the bonding system. CPN preferentially change the interface chemistry at dentin-composite.[13] Modern nanofiller self-etching primer adhesive show more bond strengths and less failure of brackets compared to conventional primers ensuring sufficient maturation of orthodontic adhesives procedures.[14] Thus, evolution in bonding system is ever going process and new technologies will always provide benefit in designing of improved and advance materials.

4. CERAMICS AND PORCELAIN

When we think of material design race for aesthetic restorations in density, ceramics and porcelain are the forerunners due to advantages of esthetics, biocompatibility, and mimicry of natural enamel properties. There has been an ever increasing demand for porcelain since their first advent for the dental restorative material, which dates back to 1960s.[15] Out of 35 million crowns placed yearly,

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71% account for porcelain due to their availability in a range of shades and translucencies for achieving lifelike natural look.[16] However, strength concerns of ceramics and porcelain compromises their use for anterior aesthetic restoration. Due to low tensile strength and brittleness, restorations are still custom made using either all-ceramic or porcelain-fused-to-metal systems without much underlying control or engineering of the microstructures. Metal inclusion in ceramic preparation reinforces second phases as a crack controlling mechanism but metal based fabrication is prone to metal discoloration and allergies.[16] Thus there is a clear need of metal base free, more crack-resistant or crack-tolerant designs in dental ceramic technology.

New material design approaches provide local control of domain properties at nano-micro interface with a novel mechanism to arrest cracks or slow down their propagation rates as crack-tolerant designs.[17] Textured layer as interwoven microstructure motifs, nano-micro particulate zirconia and alumina core have potential to minimize the stress points because different layers can be designed to have different properties (moduli) that produce crack blunting.[18–19] Micro printing and stereolithography techniques in nanotechnology provide further opportunities to control micro-nano texture of material properties of ceramics-porcelain for dental applications.

4.1. Dental Composites

The beginning phase of development in composite materials technology for the dentistry dates back to 1960s. Science of composite dental materials have advanced significantly with advent of superior filler technologies, in parallel with its bonding system and curing technologies (Fig. 3). Major revolution in composite material has been witnessed with the advent of nanofiller technologies. Previous composite restorations were prone to shrinkage and place high levels of stress on relatively immature dentin bonding films. With the combinatorial chemistry of filler and monomers, polymerization stresses are reduced evenly with interfacial stability at matrix and filler phases.[19] In addition, inter-particle distance of nanofillers causes porosity effects on fracture resistance and void sites act as water absorption reservoirs producing outstanding wetting of the filler and may primarily function in helping matrix monomers to adapt very closely to the filler at a microscopic level with silane coupling agent in nanofiller. Newer materials utilize prototype ring-opening reactions typical of epoxy systems to compensate for the double-bond reaction shrinkage; one step forward of popular silane-Si–O-substrate based chemistry that is hall mark of traditional dental composite restorations.[20] One drawback with current nanofiller technology is that due to nanoscale chemical interactions, it is impossible to measure the extent of actual chemical interaction along filler particles to further improve product chemistry. However, recent understanding of bio-physico-chemical interactions in colloidal chemistry at biomineralized-(in)organic-interface may further improve the filler technology for dental composites.[21]

4.2. Are Nano-Composite Materials Ideal Substitute to Dental Amalgam?

History of dental amalgam dates back to early 19th century and was first introduced in France. In beginning amalgam were used as substitute to gold not only due to the fact that they were considered as low cost, but also *ease* of application, strength, durability, and bacteriostatic effects were prime reasons for replacing gold.[22] Dental amalgam has reined the dental materials science as gold standard for posterior filling and considered as "black horse" of dental materials. Finding a suitable substitute to amalgam restoration due to their health hazards and aesthetic reasons, have long been debated by dental practitioner.[23] Massive research have been dedicated to find a suitable bonding systems, composites, ceramics, and esthetics material that can substitute amalgam, albeit amalgam will not disappear from the menu of dentistry due to their economic use and credible services in dentistry. However, newer composite and bonding system seems to safe and aesthetic competitor for the amalgam for the future generation dentist.[24]

4.3. Dental Cements

In traditional dental practices, cements are used for luting and bonding restorations with glass and an organic acid as native ingredients. Dental cements also get their applications as pit and fissure sealant in pedodontic care. Zinc phosphate has long been used as traditional cementing material in density but current knowledge and developments in materials sciences have impetus toward resin-based cements (resin-modified glass ionomers). Moreover, new breed of dentists are fancied towards "Universal Cements" those are hybrid of the properties of resin-modified glass ionomers and composites, designed to be self-etching using new monomer design technologies.[25] One of the subtle advantages of nano-cements compared to traditional dental cements is the improved mechanical properties in addition with gluing capabilities of cements. Incorporating nanoceramic particles (nano-hydroxy or fluoroapatite) into conventional glass-ionomer cements with N-vinylpyrrolidone containing polyacids, restorative capability tremendously improved in terms of mechanical properties.[26] In this series, Ketac™ Nano light-curing glass ionomer restorative cements is the first paste, resin-modified glass ionomer material based on bonded nanofiller technology and nano-ionomer has advantages over glass-ionomers since it provides faster, easier mixing and dispensing.[27] Another viable alternative to bis-GMA as a polymerizable matrix in the formation of bone cements has been demonstrated by developing high viscosity, self curing two paste system. A biologically active apatite layer formed on the bone cement surface

Table I. Micro-Nanoscale Features in Tooth Anatomy as Design Markers for Nanoscale Materials Fabrication.

Dental subparts	Composition	Micro-nanoscale features	References
Enamel[a]	96% mineral; hydroxyapatitie (HA) i.e., crystalline calcium phosphate; water and organic substances (proteins amelogenins, enamelins)	Microscale domains-Amelogenins Nanoscale domains: HA, water, proteins amelogenins, enamelins	[30]
Dentine	70% inorganic materials (mineralized connective tissue), 20% organic materials (collagenous proteins), and 10% water by weight	Microscale domains: dentinal tubules and odontoblasts Nanoscale features: HA, calcium phosphate, water, albumin, collagen, transferrin, tenascin, proteoglycans	[31–32]
Cementum-PDL	45% inorganic material (mainly hydroxyapatite), 33% organic material (mainly collagen) and 22% water	Microscale domains: Cementoblast Nanoscale domains: HA, water, Collagen T-1,	[31, 33]
Pulp	Cavity containing nerves, blood vessels; fibroblasts, preodontoblasts, macrophages	Microscale domains: fibroblasts and mesenchymal cells, capillaries, immune cells Nanoscale domains: water, nonspecific proteins	[34]

[a]Significant interests to materials scientist in designing enamel is its translucent properties; materials with matching refractive index to enamel is primary concern to restore aesthetics (PDL; Periodontal ligament).

within a short period after its immersion in simulated body fluid, owing to lower viscosity of urethane dimethacrylate (UDMA) which allowed better extrusion and handling properties in two paste bioactive cement.[28]

4.4. Craniofacial-Oral-Dental Anatomy: A Notion to Support Application for Material Science at Mico-Nanointerface in Dentistry

The craniofacial skeleton (TMJ, palate, jaw bone) and oro-dental parts (enamel, dentine, cementum, pulp) are basically biomineralized tissues formed by physiological biomineralization in collagenous matrices[29] (Table I). Interaction between inner neural crest–derived ecto-mesenchymal cells and overlying epithelial cells initiates differentiation of a cascade of cells involved in biomineralization and deposition of these mineralized tissues.[35] This process combines a balanced interplay of minerals and organic extracellular molecules. Viewing histological basis of this biomineralization in dental tissue reveals a particular type of calcification process, sharing a natural biomimetic modular approach at micro-nanointerface, in parallel with the bottom up approach adopted in materials sciences to fabricate micro to nanoscale moieties (Fig. 1). In recent years, materials scientists have closely explored the fields of *in vitro* biomineralization via molecular biomimetics, basically taking inspiration from natural processes.

Nanotechnology adopting synthetic routes to material design, has learnt precisely the use of tools in molecular biology to create hybrid structures for biomedicine application based on bottom up approach.[36] Particularly it is most promising for the development of advance dental materials using micro-nanotechnology based approaches since this represents tremendous potential to reconstitute artificial cell by cell based bottom-up strategy to generate entire tissue of dental anatomy via assembling tissue from enamel-dentin-cementum to pulp.[37] Moreover, as clinical and experimental evidence, it is significantly stimulating, considering the fact that assembled parts can withstand more robust masticatory forces and abrasions due to even distribution of force pressure along nano-micro interfaces.[38]

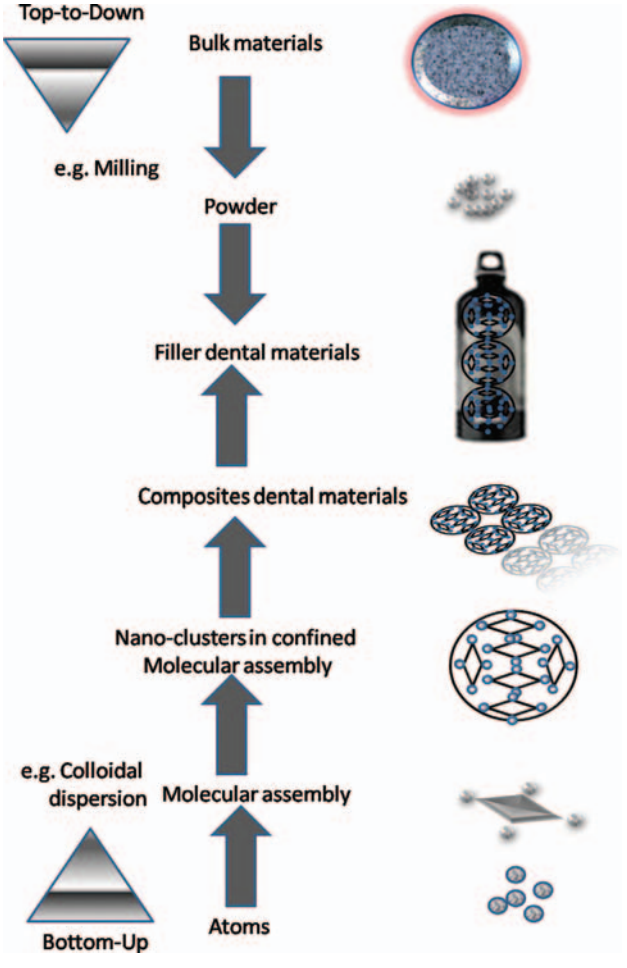

Fig. 1. Schematic illustration of top-down and bottom-up approaches to design nanofiller for clinical applications (reader should bear in mind that the schematic drawn is not to the scale and is intended to illustrate each of the main features of micro-nanoscale design).

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5. HIERARCHICAL ASSEMBLY OF BIO-ORGANIC-MINERAL COMPONENTS AT INITIAL STAGES OF MOLECULAR MINERALIZATION OF COLLAGENOUS (MINERALIZED) TISSUES OF DENTAL STRUCTURE

Membrane invested vesicles (MIVs) released by budding from the surface of odontoblasts, and cementoblasts, take the charge of initial mineralization of dentine and cementum; the collagenous mineralized dental tissue.[39] Calcium phosphate ions accumulate and start concentrating in MIVs and finally precipitate in from of HA crystals those ooze out of MIVs into extra cellular fluid as calcification nodules. Further, mineral crystals subsequently proliferate within and between collagen fibrils and rate of proliferation depends upon the presence of proteoglycans and non-collagenous ECM proteins, pH, and mineral ion concentration.[40] Molecular mechanism of biomineralization of enamel is slightly different and contrary to dentine, MIVs are absent in enamel layer and enamel mineralization occurs immediately after secretion of enamel matrix proteins from basal lamina that delimits the ameloblast layer disintegration.[41]

Later, specific proteinase are secreted those degrades proteins structuring the enamel matrix giving rise to densely knitted hardest mineralized tissue with orderly regular crystal structures. Appreciating and learning from the aforementioned molecular mineralization mechanism of enamel, Yamagishi et al. had prepared white mineralized collagenous crystalline paste of modified hydroxyapatite, which chemically and structurally resembles natural enamel.[42] Interesting fact is that it works as "quick enamel" for the repair of early carious lesions within minutes, with unique capability to reconstruct enamel without prior excavation. This could be a promising approach to painless restoration during early stages of tooth decay when the drilling and removal procedure is not ideal and proposes reoccurrence of caries formation with the tooth previous history of dental caries.[43] Morphologically, this quick acting paste contains densely packed arrays of stalked nanocrystals of hydroxyapatite formed under acidic conditions that probably acts as trigger for the fast growth of highly crystalline hydroxyapatite by dissociating the calcium phosphate clusters into calcium and phosphate ions.[44]

5.1. Nanoengineering Top-Down and Bottom-Up Approaches to Design Advance Dental Materials for Clinical Applications

In recent decades, mimicking nature's approaches in fabricating devices with similar hierarchical organization and complexity had given capability to nanosciences to design new functional materials for biomedical applications. In top-down approach, nanomaterials are generated by cutting down a complex (bulk) entity in its component parts. Contrary to this, bottom-up approach harnesses assembly of a bulk materials via molecule by molecule to produce hierarchical supramolecular assembly[45] (Fig. 1). Molecular manipulation, molecular binding, and the self assembling of biomolecules has provided remarkable elegance in designing top-down fabrication and bottom-up synthesis protocols to materials scientist.[46] Supramolecular assemblies had revolutionized guided molecular growth and controlled formation of inorganic crystal growth with nanoscale precision in controlling crystal size, growth locations and crystallographic planes.[46] These techniques have tremendous capabilities for designing advance dental materials for *in vivo* and *in vitro* clinical application for creating functional nanosuspension, nanofillers and nanohybrid composites in dentistry.[47] Few examples of nanoengineering bottom-up and top-down approaches to design advance dental materials are described below.

5.1.1. Biomimetic Approach to Biomineralization: Nature Inspired Nanoengineering Approaches to Design Dental Hard Tissue

Dental tissues are biomineralized hard structures specialized to perform mechanical functions such as mastication, cutting, grinding etc. In addition, enamel, dentin, PDL and associated structures are known to be multifunctional, serving as load bearing systems with piezoelectric material properties.[48] Looking at biochemical nature, dental histology shows that these tissues are biocomposites made up of organic structural units of macromolecules (lipids, proteins, and polysaccharides) containing nanodomain crystals (HA), protein assemblies (collagen fibers, enamel proteins) in hydrated matrix; inorganic minerals organized in well defined knitted matrix of hierarchical assembly made in natural factory.[49] Nature's bioinspired materials synthesis provides invaluable hint to material scientists to understand supramolecular mechanism of macromolecular assemblies of complex molecular crystals, micelles and membranes. Twinned hybrid material design that combines organic and inorganic components at nano-micro scale with innovative textures show controlled length, selected affinities and rich structural combinations, exhibiting unique structural and functional capabilities.[50] Considering supramolecular physics and chemistry involving hierarchical nano-mico-macro scales assemblies during secretary and maturation phases of amelogenesis and dentinogenesis, it is quite plausible to create biomineralized dental tissue.[48]

In an excellent morphogenetic approach via biomimesis, Kniep et al. had shown controlled fractal growth of fluorapatite crystals in gelatin matrices at ambient temperature where elongated hexagonal-prismatic seeds acts as nucleation sites for the crystal growth.[51] It comprises successive events of fluorapatite crystal growth followed

by morphogenetic rearrangement of crystals under pyropiezoelectricity to form core–shell structure of composite character; decalcification of these composite gives hollow spherical units which reorganize in denatured collagen (gelatin) to form ordered biomineralized crystal structures mimicking dental fluoridated enamel. This work exhibits an excellent similarity to concurrent events during biomineralization of enamel under ambient conditions and puts a strong biomimetic notion to design artificial dental structure *in vitro* based on advance material approaches.[52]

An additional nature's phenomenal capability to arrange the nanoscale (bio) organic and inorganic components to form macromolecular design of hard tissue has inspired nanoscale soft chemistry that provides researchers to carricate hybrid materials with controlled organic–inorganic interfaces, original hybrid materials with controlled porosity and/or texture.[53–54] These design features are remarkably interesting to fabricate dental materials for advanced applications with advantageous tunable physical properties, high photochemical and thermal stability, chemical inertness and negligible swelling. These both in aqueous and organic solvents which are of paramount importance for *in vitro* morphogenesis and restorative material design for clinical practices.[55]

In recent years, many studies related with biomineralization of dental tissue have been persuaded like, nature inspired biomimetic approaches to control *in vitro* morphogenesis, crystal growth, and biophysical properties under ambient conditions. In addition, researchers have borrowed nature's concept from bone and enamel mineralization for the controlled growth of hybrid organic–inorganic components to design biomineralized tissues.[56] Designing artificial nanocomposite system of fluoridated hydroxyapatite crystals and amelogenin for controlled interaction in sequential stages of supramolecular organization and spatial patterning; interfacial molecular recognition in inorganic nucleation; vectorial crystallization; pattern evolution and hierarchy, provides controlled growth of needle like crystal similar to DEJ junctions.[52,57] *In vitro* nanoengineering based biomimetic approaches also provide control over microenvironment such as pH and degree of ionic saturation which are utterly critical for amelogenic control over HA crystal growth for reparative dental procedure.[58] Moreover, it is plausible to design histological dentine *in vitro* using biomimetically mineralized 3-D scaffold of hydroxyapatite-collagen composite exhibiting an *in vivo* interconnecting pore structure and elastic mechanical properties.[59]

5.1.2. Mineral Binding Peptides, Protein, DNA Assembly: Gluing Inorganic Structures with Biomolecules

Learning from molecular biomimetics, researchers have precisely decoded the role of proteins, DNA and peptide motifs in controlling the structures and functions of biological hard and soft tissues in organisms.[60] Performing myriad of functions from uniformly self and co-assembled subunits into short and long-range-ordered structures to develop variety of tissue in biological system, proteins and DNA are the most obvious choice for next-generation biomimetic systems based materials design at bio/micro-nanointerfaces.[61] In hierarchical organization of biomaterials *in vivo*, proteins play all-important role from the molecular to the nano-micro-macro scales organization, designing complex tissues under physiological conditions using biomacromolecules. Based on molecular recognition and self-assembly and DNA manipulation, scientists have explored genetically engineered proteins for inorganics (GEPIs) which are used as blueprint for creating functional hybrid structures such as inorganic-protein building blocks at nano-micro interface for advance material applications[36] (Fig. 2). The combinatorial chemistry provides a unique method to design the metal binding GEPIs libraries based on recognition properties of proteins under the premises of inorganic surface-specific polypeptides which could be used as binding agents to control the organization and specific functions of materials. Moreover, combinatorial

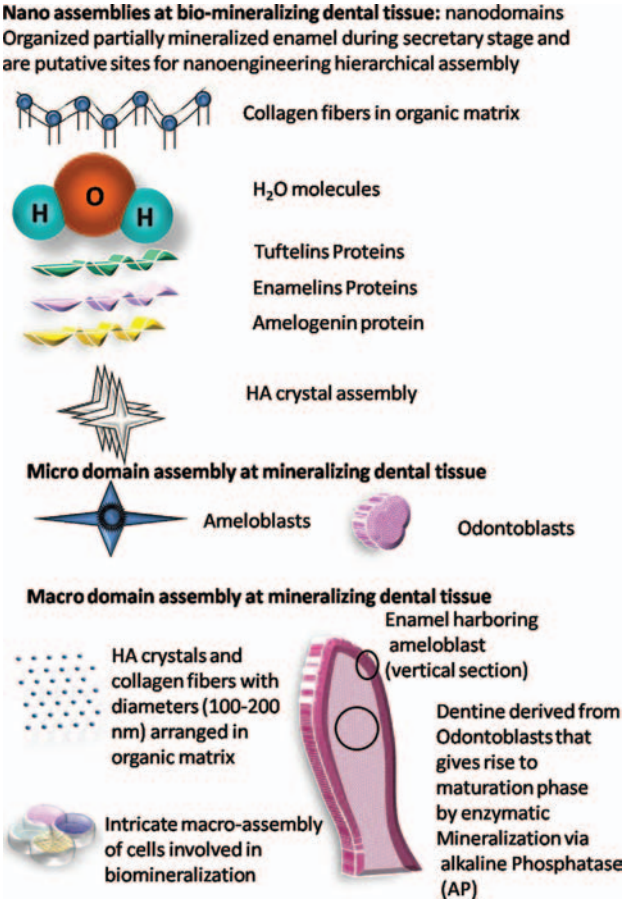

Fig. 2. Nano-micro-macroscale assembly of bio-inorganic structure of biomineralized dental hard tissue as putative structural cue to design advance dental materials for clinical applications.

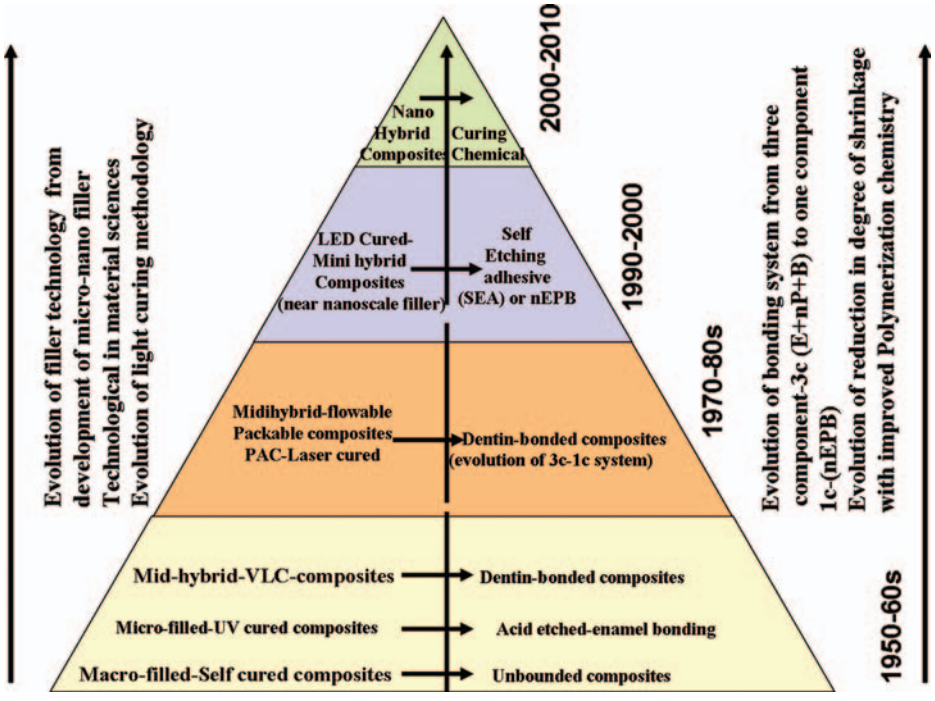

Fig. 3. Trend line showing evolution of different dental materials for clinical application with advances in materials sciences in past, present and near future.

protocols provide a novel opportunity to select polypeptide sequences that preferentially bind to the surfaces of inorganic compounds such as ZnO/$CaCO_3$/SiO, specifically chosen for the design of advance dental materials applications, based on chemical specificity of GEPIs selected.[62–64] In addition, GEPIs-protein mediated bottom up assembly of biomineralized tissue *in vitro* mimicks control of crystal growth at nano-micro interface precisely as

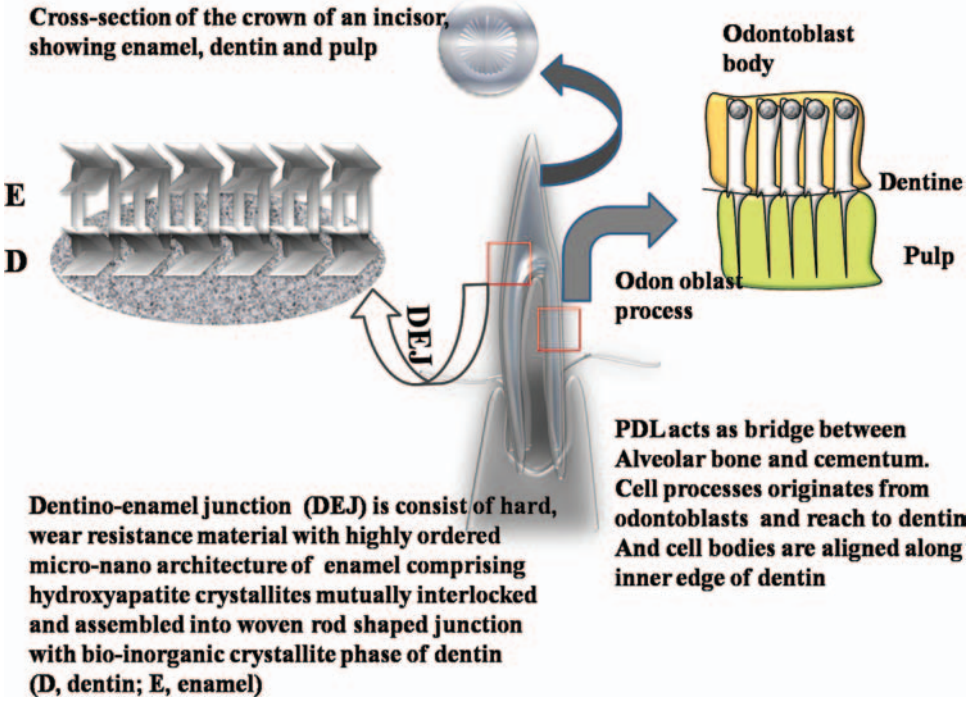

Fig. 4. Histological features of biomineralized micro-nanointerface of tooth anatomy as putative structural analogue to design *in vitro* enamel, dentin and other tooth structures via biomimetic approach of biomineralization (schematic drawn are not to the scale).

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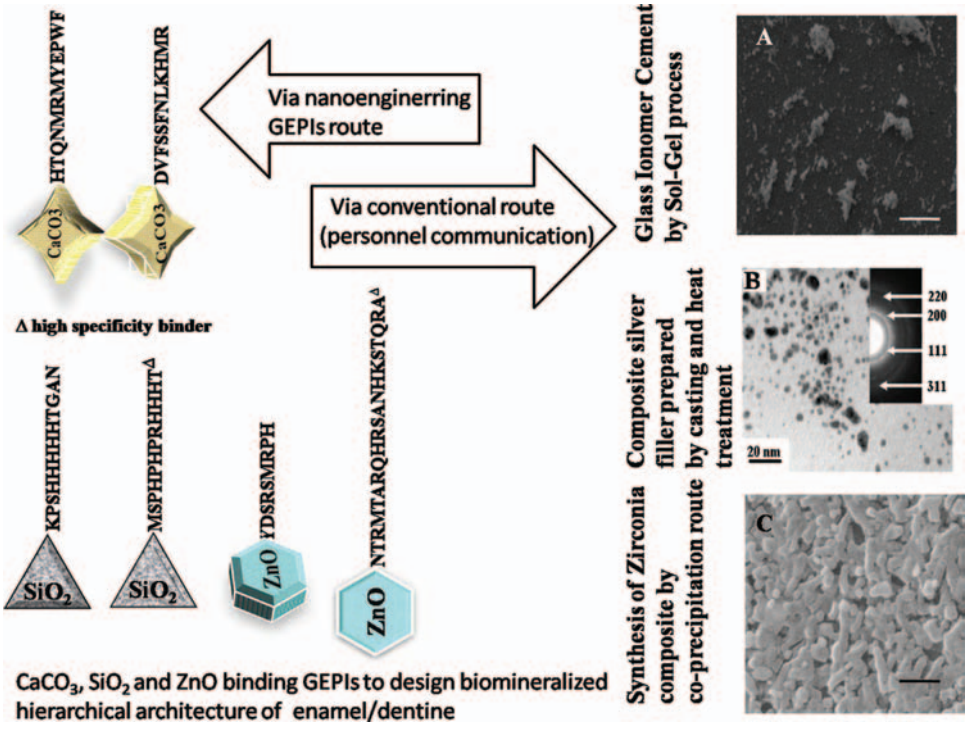

Fig. 5. Comparison of conventional dental material design recipes with nanoengineered GEPIs for designing nanoscale hybrid biomineralized scaffolds of tooth. Left panel: GEPIs synthesized via biomimetic nanoengineering approaches, bind to inorganic crystals like $CaCO_3$, ZnO and silica provide unique opportunity to control crystal growth, orientation and crystallographic planes of filler nanomaterials. Right panel A–C: three exemplary physic-chemical routes to conventional dental material synthesis (figure A–C: AV Singh and WN Gade, personal communication; scale bar in figure A, C: 20 μm).

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biological control over materials formation through protein/inorganic interaction. Thus, GEPIs linked to enamel-dentine protein could build mineralized tissue *in vitro* by joining synthetic building block.[65] Moreover, GEPIs could be chemically linked to conductive or light sensitive polymers with unique functional properties specific to enamel or dentine restoration as multifunctional hybrid polymeric units. In another interesting self assembly based fabrication of mineralized tissue, researchers have designed pH-induced self-assembly of a peptide-amphiphile to make robust nanostructured fibrous scaffold reminiscent of extracellular matrix. Peptide-amphiphile allows the nanofibers to be reversibly cross linked and initiate direct mineralization of hydroxyapatite to form a composite material. Crystallographic axes of mineralized tissue shows similarity with natural bones.[66] Using GEPIs mediated bottom up approach, virus capsids with three distinct surfaces (inside, outside, interface) can be exploited to generate nanomaterials with multiple functionality by design to create a library of protein cage architectures as dental materials at micro-nanointerface of tooth anatomy (CEJ, DEJ) for advance applications.[67] This simple approach of *in vitro* biomineralization opens a unique opportunity to fabricate natural tissues of dental origin under ambient laboratory conditions.

In last decade, self assembled or pre-organized molecular or supramolecular moulds of bio-organic (possibly biological peptide, protein, DNA) have been vastly discovered as building blocks to design structural and functional hybrid molecules.[37] Based on their chemical specificity and *in vivo* molecular recognition capability to recognize inorganic binding ligand, particularly peptide motifs and proteins have been used as design scaffolds to control molecular behavior of biomaterials for advance biomedicine applications.[36, 68]

As described above, combinatorial chemistry approach, based on bacterial cell surface and phage-display technologies to develop mineral binding GEPIs as blueprint for manufacturing hierarchical functional hybrid specific to dental material applications provides a unique possibility to design novel dental materials, based on bottom-up approach.[36] Adopting similar approaches, functional hybrids of polysaccharides;[69] proteins;[70] enzymes[70–71] and DNA have been developed. More interestingly, wrapped biomolecules remain structurally intact and maintain their functionality even under adverse conditions.[72]

So far, manufacturers of dental materials heavily rely on energy intensive coupling chemical routes to innovate nanofillers, nanocrystal, nanocomposites and resin bonding system.[73] When designing synthesis recipe for materials science, one need to consider synergistic collaboration of structure-function relationship closely, as does the nature in its language of shape to communicate specific function. Moreover, the performance of a

material depends not only on its formulation but also on an optimized process. Adopting biomimetic nanoengineering approaches, entailing organic–inorganic hybrids via biological supramolecular chemistry, is most promising in designing biomineralized tissue of dental origin as these provide excellent control over crystal growth, material morphology and uniformity.[74]

5.1.3. Synergetic Co-Assembly of Nanoparticles on Molecular Precursor and Moulds

This approach invites to assemble nanoparticles on molecular precursors (either biopolymers) or moulds (inorganic) those acts as seed for further growth of individual particles to form different shape and sizes in colloidal suspensions.[75]

This is particularly simulative for dental material design because of control over mechanistic growth of 2D or 3D growth depending upon precursor specific application design of purely mineralized (enamel) or biomineralized (dentin) materials.[76] Moreover, synergetic co-assembly of nanoparticles on molecular precursor and moulds provides an opportunity to tailor properties and functionalities via crystallinity engineering to achieve monodisperse nanoparticle depending upon molecular architecture of precursor/mould template.[77] Since surface microstructure, texture and porosity vitally controls the mechanical properties of materials for advance dental application, hence physical approaches to dental material design should have tight control over nanoparticles/nanocomposite synthetic routes that have been explored vastly in recent years.[78]

An interesting synergetic approach for dental materials synthesis based on above described technique is utilizing different zwitterionic states of protein at different pH for synergetic co-assembly of two different minerals.[79] Moreover, playing around the binding strategy of minerals with precursor biomolecules depending on their redox potential, one can design vast array of nanofiller and nanostructure alloy for advance dental restorative application.[80]

Another area of nano-engineering based dental material synthesis is *in situ* polymerization which includes urea-formaldehyde (UF) and melamine formaldehyde (MF) encapsulation systems in polymerization mixtures to covalently couple nanohydroxyapatite (*n*HAp). In one such approach Khan et al. have utilized electrospinning process for the development of bioactive nano-fibers as promising restorative materials.[81] In their work, coupling *in situ* polymerization with electrospinning technique has given an advantage to control Ca^{+2} concentration and distributions in *n*HAp-UF polymerization mixture which stimulates osteoblastic proliferation and depresses osteoclast-mediated bone resorption. Nanofibers produced by the electrospinning technique have high porosity on the submicrometre length scale with high-surface-area to volume ratio which provides guided bone regeneration

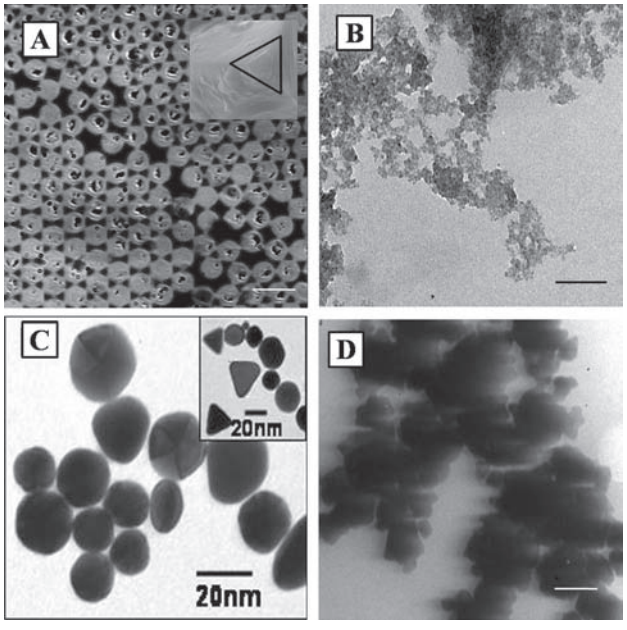

Fig. 6. Dental material designed via different nanoengineering approaches showing versatile structural features for clinical applications (personal communication). (A) Templated biomimetic synthesis of $CaCO_3$ crystals using protein assemblies (Inset: triangular apex geometry of crystal; scale bar: 50 nm). (B) Synergetic co-assembly of silver fillers using Poly-L-Lactic acid (PLA) polymer precursor (scale bar: 100 nm). (C) Morphosynthesis of spherical, quasi-spherical and triangular silver NPs in confined biomolecular geometry bovine serum albumin (BSA) foam[80] (Inset: triangular NPs; scale bar: 20 nm). (D) Integrative synthesis of Au–Ag alloy using zwitterionic characteristic of BSA and capping with bioactive growth factor[79] (scale bar: 50 nm).

and scaffolding. Moreover, electrospinning is superior to other conventional techniques with respect to morphology control of electrospun nano-fibres via controlling ambient parameters such as temperature, humidity and air velocity in the electrospinning chamber and viscosity, conductivity and surface tension, hydrostatic pressure in the capillary.[82]

5.1.4. Morphosynthesis via Chemical Transformations in Confined Geometries

Morphosynthesis refers to mineralization via controlled chemical transformations in confined geometries (microemulsions, micelles and vesicles) using double hydrophilic block copolymers which contain a molecular head reacting with the metal and a central non reactive part similar to proteins containing hydrophilic and mineralophilic sites.[83] Morphosysnthesis in confined geometry might be very valuable tool to design biomineralized nanofiller materials for restorative dentistry mimicking alignment of mineralized collagen fibrils distributed along dentinal tubules in dentin or aligned crystal pattern along DEJ.[84] Microemulsion, liquid crystal and block copolymer template-directed morphosynthesis provides rare opportunities to design biologically programmed inorganic–organic hybrid nanoscale materials that can be

Table II. Commercial nanoscale products for advance dental materials application.

Nano scale Recipe	Technique	Applications	Advantages	References	Trade name
Lidociane-nanogel hybrid[a]	Bottom up approach	Drug delivery system for LA	Prolonged infiltration anesthesia	[90]	Pluronic® F-127(Nanogel)
Nano-dentifrices[a]	Dentifrice containing nano-sized carbonate apatite (*n*-CAP)	Desensitizing dentifrices	Higher occlusion to the dentinal tubules	[91]	JOROKARUSO™
Nano-fillers[b]	Aluminosilicates nano-powder with average size 50–100 nm (Al:Si as per clinicla requirement)	Restorative and bonding agent	Superior hardness; modulus of elasticity aesthetic (translucency with matching dentine RI)	[92]	Tokuyama™
Nanocomposites[a]	Agglomerated discrete nanoparticles, capped with stabilizing; agents and distributed in resins or coating agents as per specific restorative application	Glass ionomer cement; Resin cement, dental lining; Resin modified glass ionomer	Excellent handling properties, reduced; filling shrinkage, higher translucency and cosmetic properties for anterior aesthetic; restoration, superior mechanical strength	[93–96]	Artiste™, Filtek Supreme™; Restorative pure nano; CeramX™
Nano-hybrid composites[a]	Nano-micro hybrid system made by coupling chemistry	Superior flexural-compressive strength, color stability	Composite restorative materials	[97]	Simile™
Nanosolution as adhesive[b]	10% by weight, 5–20 nm Silica nanoparticles in colloidal suspension	Adhesive agent for restorative purposes	No clumping of solution (no shake solvent), higher dentine bond strength	[98]	Nano-Bond™ Adper™ single bond plus adhesive
Nano elastomer[a]	Hydrophilic nanopolymers with elastic properties	Impression materials	Excellent elastic recovery; high dimensional stability; high deformation strength	[99]	Zhermack Elite™ HD + VPS
Antimicrobial barrier dressing[a]	Cationic Ag NPs loaded mesh	Antimicrobial dressing	Controlled release of therapeutics; more penetration to microbial cell membrane by cationic NPs	[100]	ACTICOAT[a]
ECM protein scaffolds[a]	Enamel matrix and amelogenins of various molecular Weights.	PDL regeneration	Tissue regeneration with minimal gingival recession	[101]	Emdogain®
Bone replacement materials[b]	Bone Morphogenic Protein (BMP) + HA scaffolds	Cell differentiation in PDL pathologies	Higher tissue regeneration	[102]	VITOSS®
Nanotweezers/micro-nano-needles[b]	RCT treatment and Veneering applications	Surgical aids	Higher biocompatibility, provide access in remote areas of dental defects	[103]	NanoPass™ technologies; Sandvick Bioline, Nanotweezers™
Nano scale ECM assembly gel[a]	Synthetic 16-amino-acid peptide, forming nanofibres	Delivering therapeutic proteins and stem cells in a localized dental bone defects	Superior regeneration over fracture cements	[104]	PuraMatrix™
β-Tricalcium Phosphate (TCP) NPs-growth factor assemblies in paste[b]	β-TCP particles and recombinant human platelet-derived growth factor-BB (PDGF-BB)	Injectable bone graft	Injectable bioactive ingredient for PDL and TMJ fracture	[104]	GEM 21S™, Biomimetic Therapeutics
Hydroxyapatite paste[b]	Nanocrystalline HA paste	Orthodontic facial surgery	Wound healing with bone regeneration	[105]	PerOssal®
Nano-hybrid restorative material for all dentin/enamel bonding[a]	Coupling chemistry linked nanofiborus materials	Orthodontic bonding agent	Good susceptibility and high abrasion resistance, enhanced color stability	[106]	Grandio®

[a]Manufactured by Bottom-up nanoassembly approaches. [b]Manufactured by top-down nanoassembly approaches.

self-assembled into high-ordered superstructures for dental applications.[85] In near future, morphosynthesis will provide even more possibilities with synthetic recipes for metal sintering, the moulding of thermoplastic materials, processing of multifunctional materials and ceramic objects for dental application with more biocompatibility.

5.1.5. Integrative Synthesis to Design Smart Bioactive Dental Material at Biology/Material Interface

As the word integrative indicates, this method utilizes any of the above nanoengineering processes to design bioactive dental materials rather than conventional bioinert restorative dental materials. Generally bioactive coating is common practice in dental implantology, we limit our discussion to integrative methods to design bioactive restorative or filling materials, as discussion about dental implant in itself is vast topic and is beyond the reach of present overview of nanoengineering approaches discussed here.

Bioactive glass/ceramic/composites application in restorative dentistry are not new, however, new nanoengineering approaches could provide superior next generation dental materials with ability to cross talk the cellular flora of dentin/enamel (odontoblast, ameloblast) as a stimulus to initiate biomineralization during chronic dental pathologies.[86] Classical integrative synthesis methods for dental composites have used matrix phases with diluents in different proportions of silanized hydroxyapatite fillers to improve mechanical properties.[87] In addition, reports showing disparity in water absorption behavior of untreated and surface-treated hydroxyapatite (HA) could be vital cues to improve the restorative applications via integrative approaches such as controlling porosity and filler particle aggregates in the microstructure of composites.[88] However, issues related with bioactivity were the main concern for the clinicians based upon the classical integrative methods. Present day engineered electrospun nanofibres, with bioactive ceramic/composites scaffold designed by integrative approaches contains cell instructive ECM peptide analogue (RGD, IVKAV) favoring *in situ* biomineralized tissue formation via apatite hydroxyl-carbonate crystallization under active cell proliferation and differentiation.[89]

New paradigm in dentistry is shifting from "bioinert to bioactive" dental materials towards design of three-dimensional innovative composites as 'smart' materials such as cements or bio-cements, nanofillers and composites with the controlled shrinkage over time, capacity for self-repair or self filling upon post restorative microleakage. Table II gives an overview of current generation nanomaterials designed on the basis of nanoengineering approaches and used as commercial nanoproducts for advance applications in restorative dentistry.

6. CHALLENGES IN ADVANCE DENTAL MATERIAL DESIGN

Toxicity (systemic, genotoxicity, carcinogenicity, reproductive toxicology) to clinicians-patient due to micro-nanoscale design

Feasibility of scaling up from research levels to industrial output

Failsafe design with longevity

Batch-to-batch repeatability in production;

Ethical concern if any

Methods to achieve and maintain sterility;

Tissue procurement for cell preparations;

Test for local effects after restoration (long-short term)

Longevity of new materials

Test for irritation and sensitization

Selection of tests for interaction with blood vessels and nerves in pulp chamber.

7. CONCLUDING REMARK

In the near future, materials showing higher elasticity, improved plastic deformation and fracture resistance should be obtained by coupling synthetic methods with molecular processing techniques. Moreover, the influence of confinement on the dynamics of macromolecules (natural and synthetic) trapped in aggregates or inorganic or hybrid lattices (mesoporous or lamellar hosts, and so on) and on the mechanical properties of nanocomposites has not been sufficiently studied. In the long term even more possibilities exist: metal sintering, the moulding of thermoplastic materials, processing of multifunctional materials, those ideally would revolutionize the science and art of dental materials science, riding on the wave of current nanoengineering approaches.

CONFLICT OF INTERESTS

The authors state no conflict of interest.

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