

Calcium fluoride-based dental nanocomposites

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2.1 Introduction

The paper presented by Nobel Laureate Dr. Richard Philips Feynman in 1959 at the annual meeting of The American Physical Society at the California Institute of Technology introduced something to the world that had always existed, but had somehow escaped human curiosity [1, 2]. This concept was first termed “nanotechnology” by N. Taniguchi in 1974, who also described it as “the processing of, separation, consolidation, and deformation of materials by one atom or by one molecule” [3]. The potential of nanotechnology was further reinforced by the works of K. Eric Drexler based on molecular machinery, manufacturing, and computation in the 1980s [4]. The idea of nanotechnology is based on the manipulation of matters on the atomic, molecular, and supramolecular levels [5]. According to the definition of the National Nanotechnology Initiative, nanotechnology is the manipulation of matter with at least one dimension sized between 1 and 100 nm (1 nm = 1 billionth of a meter or 10^{-9} of a meter) [6]. At present, nanotechnology research is acknowledged as one of the flourishing science and technological research areas [7, 8]. The recent nanotechnological research in biomaterial sciences comprises development of nanoparticles, nanocapsules, nanovesicles, nanoceramics, composites, nanocomposites, nanofibers, nanocoatings, nanotubes, nanorods, and so forth [9–30]. Nanotechnology has been utilized in various biomedical applications, such as dentistry, orthopedics, tissue engineering, wound healing, antimicrobials, drug delivery, stem cell therapy, cancer therapy, biosensors, diagnostics, and so forth [7, 8, 31–38]. With the advancement of nanotechnological research and development, newer nanobiomaterials are being fabricated and evaluated for use in dentistry. These are mainly utilized in dentistry as dental implantable materials, dental restorative materials, dental nanorobots, denture teeth, periodontal drug delivery materials, and so forth [39–43]. Currently, numerous dental nanocomposites are being designed and tested that are greatly contributing to the steady development of nanodentistry [44]. Among these dental nanocomposites, inorganic-inorganic nanocomposites are preferred to meet the mechanical strength required for dental biomaterials. Important inorganic dental biomaterials being exploited for the design and

development of dental nanocomposites include calcium fluoride (CaF_2) [32], calcium phosphate (CaPO_4) [45, 46], hydroxyapatite [47, 48], bioactive glass [49], and so forth. CaF_2 is one of the inorganic biomaterials widely used in dentistry to design dental nanocomposites [32, 50]. This chapter presents a comprehensive review of CaF_2 -based nanocomposites in dentistry.

2.2 Nanocomposites

A composite is a mixture of two or more different materials that are combined to achieve properties that are superior to each of the constituents [51]. A nanocomposite is a multi-phase solid material in which one of the phases has one, two, or three dimensions of less than 100 nm, or a structure with repeated nanoscale distances between each of the different phases that make up the material [52]. Nanocomposites are mainly multiple nanomaterials, or nanomaterials incorporated into another bulk material [53]. The phases of nanocomposites may be inorganic-inorganic, inorganic-organic, or organic-organic. Nanoparticles can be employed to form a nanocomposite, for example, nanohybrid or nanofilled composites. Nanocomposites possess better finishing, polishing ability, shade matching, flexural strength, and hardness as compared with conventional composites [52, 53]. Advantages of nanocomposites over conventional composites are [53, 54]:

- i. increased hardness
- ii. improved flexural strength
- iii. improved toughness
- iv. high polish retention
- v. higher translucency
- vi. exceptional handling properties and
- vii. decreased polymerization shrinkage (in the case of polymer-based nanocomposites)

2.3 Classification of nanocomposites

Nanocomposites can be broadly classified into two main categories:

(1) polymer-based and (2) nonpolymer based.

2.3.1 Polymer based

In the polymer-based nanocomposites, the electrical, optical, mechanical, and catalytic characteristics are attributed by the inorganic materials and the polymeric matrix, which influence enhanced thermal characteristics and mechanical stability [55, 56]. These are processed by different ways, such as solution intercalation, in situ intercalative polymerization, melt-intercalation, template synthesis, and sol-gel synthesis [57]. These polymer-based nanocomposites have been categorized as [54, 56, 57]:

- Polymer/ceramic nanocomposites: for example, chitosan-pectin-titanium dioxide (TiO_2) nanocomposite, K-carrageenan/calcium phosphate nanocomposite, bacterial cellulose/hydroxyapatite nanocomposites.

- Inorganic/organic polymer nanocomposites (clusters): for example, polymer nanofiber with zero valency nanoparticles.
- Inorganic/organic hybrid nanocomposites (nanocrystal): for example, cadmium sulfate nanocrystals.
- Polymer/layered silicate nanocomposites: for example, nylon-6/montmorillonite nanocomposites, montmorillonite-alginate nanocomposites.
- Polymer/polymer nanocomposites: for example, chitosan-starch nanocomposites, nanocrystalline cellulose-fibrin nanocomposites.

Depending on the composition and inherent characteristics, polymer-based nanocomposites have exhibited improved mechanical properties such as tensile strength, toughness, thermal expansion and conductivity, ablation resistance, chemical resistance, and so forth [55]. Inorganic materials (metals or ceramics) provide and maintain the mechanical properties of the polymer matrices supporting cellular mechanisms. Thus, as documented in various clinical cases in dentistry, these may be used as substitutions of indigenous tissue. In recent years, the development of various polymer/ceramic nanocomposites has offered promising prospects in the field of dentistry due to their ability to regenerate of pulp-dentin complexes, periodontal ligaments, alveolar bones, and to serve as a probable substitute for enamel, and so forth [44, 56, 58].

2.3.2 Nonpolymer based

In nonpolymer based nanocomposites, the compositions do not contain any polymers or polymer-derived materials. These are often called inorganic nanocomposites [56, 59]. These nonpolymer based nanocomposites can be further categorized into metal-based nanocomposites and ceramic-based nanocomposites.

Metal-based nanocomposites are characterized by:

- increased strength and hardness
- lesser melting points
- super plasticity
- increased miscibility of nonequilibrium components in alloying and solid solutions
- improved magnetic properties
- increased electrical resistivity (because of increased disordered grain surfaces)

Ceramic-based nanocomposites are characterized by:

- increased strength and hardness
- better toughness
- ablation resistance because of refined particle size
- increased ductility

The nonpolymer based nanocomposites are also classified as: metal/metal nanocomposites (either in form of alloy or core shell structure): for example, Pt-Ru nanocomposites, ceramic/ceramic nanocomposites: for example, calcium sulfate-biomimetic apatite nanocomposites, zirconia-alumina nanocomposites, metal/ceramic nanocomposites (either in form of nanotube or complicated nanostructure): for example, hydroxyapatite/titania nanocomposites, hydroxyapatite-magnetite nanocomposites, and hydroxyapatite-titanium dioxide (TiO_2) nanocomposites.

In the nonpolymer based nanocomposites, inorganic materials (metals or ceramics) such as bioactive glass nanoparticles, calcium phosphate, hydroxyapatite, and so forth, are beneficial in relation to dentin-pulp complex regeneration [58]. Dentin-pulp regeneration, alveolar bone regeneration, and enamel substitution are the areas in dentistry in which the applications of metal-based nanocomposites and ceramic-based nanocomposites offer promising prospects [44, 58].

2.4 Nanocomposites in biomedical applications

During the past few decades, nanocomposites have been designed for use in various important biomedical applications such as dentistry, orthopedics, tissue engineering, wound healing, antimicrobials, drug delivery, stem cell therapy, cancer therapy, biosensors, diagnostics, and so forth [24, 26, 44, 58, 60–65]. Examples of nanocomposites used in important biomedical applications are summarized in Table 2.1.

Table 2.1 Examples of nanocomposites used in biomedical applications

Applications	Nanocomposites	References
Dentistry	Chitosan/carboxymethyl starch/montmorillonite nanocomposites (for reduction of dental bacterial biofilm formation)	[66]
	Chitosan and dicalcium phosphate on tricalcium silicate-based nanocomposites (for root-end dental application)	[67]
	CaPO ₄ and CaF ₂ dental nanocomposites	[32]
	CaF ₂ based dental nanocomposite	[46]
Orthopedic	Porous chemically cross-linked poly(ϵ -caprolactone)-hydroxyapatite nanocomposite scaffold (to repair a mandibular bone defect)	[68]
	Hydroxyapatite-mullite composites (for orthopedic implantation)	[69]
Tissue engineering	Gelatin-hydroxyapatite nanocomposite scaffolds	[60]
	Bioactive glass ceramic nanoparticles disseminated chitosan nanocomposite scaffolds	[70]
Drug delivery	Chitosan-starch nanocomposite particles (for delivery of bis-desmethoxy curcumin analog)	[71]
	Montmorillonite-alginate nanocomposite (for releasing of irinotecan)	[72]
	Sodium alginate/nanohydroxyapatite nanocomposite beads (for sustained releasing of diclofenac sodium)	[73]
	Nanohydroxyapatite-antibiotic composites (as bone-implantable drug delivery)	[74–78]

Table 2.1 Continued

Applications	Nanocomposites	References
Stem cell therapy	Chemically modified bacterial cellulose nanocomposite	[79]
Cardiac prosthesis	Modified polyhedral oligomeric silsesquioxane-nanocomposites (in heart valve prosthesis having self-endothelialization potential)	[80]
	Poly(vinyl alcohol)-bacterial cellulose nanocomposites (in mechanical aortic heart valve prosthesis)	[81]
Artificial blood vessels	Nanocrystalline cellulose-fibrin nanocomposites (for artificial vascular graft applications)	[82]
Cancer therapy	Fe ₃ O ₄ -hydroxyapatite nanocomposites (for potential bone cancer therapy)	[83]
Wound healing	Chitosan-poly(vinyl alcohol)-TiO ₂ nanocomposite (as wound dressing)	[84]
	Alginate/Ag/nicotinamide nanocomposites (for treating diabetic wounds)	[38]
	Bacterial cellulose-ZnO nanocomposites (as dressing system for burn wounds)	[85]
Antimicrobial properties	Zn-mineralized alginate nanocomposites	[86]
Biosensors	Grafted sugarcane bagasse/Ag nanocomposites	[23]
	Graphene/polyvinylpyrrolidone/polyaniline nanocomposite (cholesterol biosensor)	[87]

In dentistry, an acceptable substitute for human tooth tissues should resemble the chemical and physico-mechanical characteristics of the natural tooth, which can be replaced or utilized as dental restorative materials, dental nanorobots, denture teeth, dental implantable materials, periodontal drug delivery materials, and so forth [39–43]. Varieties of nanocomposites are being developed for dentin-pulp regeneration, alveolar bone regeneration, enamel substitution, periodontal ligament regeneration, periodontal drug delivery, and so forth [44, 58, 88]. In most of cases, dental nanocomposites are being fabricated using resin materials and inorganic materials such as bioactive glass ceramics, CaF₂, CaPO₄, hydroxyapatite, metals, and so forth [44, 58]. Use or incorporation of inorganic materials in the composition of dental nanocomposite formulas should be beneficial for achieving improved mechanical properties such as tensile strength, toughness, chemical resistance, ablation resistance, and so forth [55, 56].

2.5 Calcium fluoride (CaF₂) and its use in dentistry

CaF₂ is a calcium salt, also called fluorspar. It is insoluble solid material. CaF₂ occurs as the mineral fluorite and crystallizes in a cubic motif (i.e., fluorite structure) [89]. In the crystal of CaF₂, Ca²⁺ centers are 8 coordinate, being centered in a “box” for 8 fluoride centers [90]. In addition, each fluoride center is coordinated to the 4 Ca²⁺ centers.

Although perfectly packed crystalline samples of CaF_2 are colorless, but impure; CaF_2 are often deeply colored owing to the presence of impurities [89].

CaF_2 is recognized as an important dental material used in fluoride treatments. In dentistry, lower concentrations of CaF_2 have a positive effect on both enamel and dentin demineralization and re-mineralization [91]. CaF_2 deposits actually act in such a manner because of a surface covering of $-\text{PO}_4$ ions and/or proteins, which makes CaF_2 less soluble under in vivo conditions, as compared with a pure state in the inorganic solutions. In addition, because of the $-\text{PO}_4$ groups on the CaF_2 surface, fluoride is supposed to be discharged with declining pH milieu, when the $-\text{PO}_4$ groups are protonated in the dental plaque. For effectual fluoride treatments, fluoride needs to be deposited and gradually released [92]. In dental applications, CaF_2 is extensively utilized, especially in restorative dentistry. The two most common hindrances in restorative dentistry are the marginal breakdown of restoration, leading to secondary/recurrent caries and the fracture of restoration [93]. Studies have shown that sustained release of fluoride ions helps in combating the demineralization process of enamel and dentin, further preventing secondary caries [94, 95]. Fluoride ions are capable of inhibiting demineralization, as well as promoting remineralization. Mineralization by fluoride ions is aided by the availability of calcium ions.

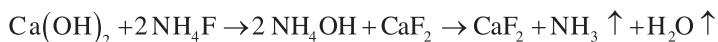
2.6 Calcium fluoride (CaF_2) nanocomposites in dentistry

With the expansion and progress of nanoscience and nanotechnology, newer nanobiomaterials are being explored for use in a range of biomedical purposes, including dentistry. Among these newly developed nanobiomaterials, nanocomposites are the group comprised of multiple nanoscale materials, or a nanoscale material incorporated into the bulk materials. In dentistry, and hard tissue engineering applications, inorganic nanocomposites are preferred over polymeric nanocomposites to meet the required mechanical characteristics [44, 55, 56]. The inorganic materials that are used to formulate dental nanocomposites are CaF_2 [32], CaPO_4 [46, 74], hydroxyapatite [48], bioactive glass [49], and so forth. In recent years, CaF_2 has been used to develop various nanocomposites for dental applications [32, 50].

In their research, Xu et al. developed CaF_2 -based dental nanocomposites through incorporating CaF_2 nanoparticles into the dental resin. In this research, three hypotheses were tested: (a) a resin composite containing CaF_2 nanoparticles would have sustained the release of high levels of fluoride; (b) a composite containing both CaF_2 nanoparticles and CaPO_4 nanoparticles would release not only fluoride, but also calcium and phosphate ions; (c) a composite containing both nanoparticles (CaF_2 nanoparticles and CaPO_4 nanoparticles) and reinforcing fillers would have high levels of ion release, as well as high mechanical properties. The fluoride releasing capacity of the CaF_2 based nanocomposite was matched, or surpassed, the reported releases from traditional glass ionomer or resin-modified glass ionomer (RMGI) materials. The strength and elastic modulus of the newly developed nanocomposites matched those of commercial stress-bearing nonreleasing composites. The mechanical properties and the ion release of the nanocomposites could be modified by guiding the nanoparticle filler level and

the reinforcing filler level. In this research, the newly developed CaF_2 -based dental nanocomposites were found to be competent, having both superior mechanical, as well as fluoride releasing, properties.

Xu et al. prepared a CaF_2 nanopowder using a spray-drying system [32]. In this methodology, a calcium hydroxide [$\text{Ca}(\text{OH})_2$] solution (2 mM/L) and an ammonium fluoride (NH_4F) solution (4 mM/L) were prepared and simultaneously fed into a two-liquid nozzle that permitted mixing of the two solutions at the time of atomization. The reaction led to the formation of ammonium hydroxide (NH_4OH) and CaF_2 . The suspended CaF_2 nanoparticles were trapped in the electrostatic precipitator and collected at the end of the process. NH_4OH was removed as NH_3 and H_2O vapors with the air flow.



During some studies, composites belonging to three groups were used to examine the effect of the CaF_2 /whisker ratio on the mechanical properties of a composite containing whiskers and CaF_2 and dicalcium phosphate anhydrous (DCPA) nanoparticles, and to measure the ion release for the nanocomposite [96–98].

CaF_2 nanoparticles were characterized by powder X-ray diffraction (P-XRD) analysis (to detect the phase of the nanoparticles) and transmission electron microscopy (TEM) analysis (to visualize morphology of the nanoparticles). The P-XRD analysis demonstrated the feasibility of synthesizing CaF_2 nanoparticles using the two-liquid nozzle spray-drying approach. Compared with its highly crystalline macrocounterpart, the CaF_2 nanopowder had broader peaks, denoting that the CaF_2 was present in a relatively poorly-crystalline phase. Multipoint BET (Brunauer, Emmett, and Teller) particle surface area analyses were also performed in these studies. The BET measurement for the CaF_2 nanopowder yielded a specific surface area of $35.50 \text{ m}^2/\text{g}$, the density of CaF_2 nanoparticles measured $\rho = 3.18 \text{ g/cm}^3$; while the diameter of the CaF_2 nanoparticle was $d = 6/(A_p) = 53 \text{ nm}$ [32]. The morphology of CaF_2 nanoparticles was visualized by a typical TEM photograph (Fig. 2.1), and at a higher magnification, the particles showed many spherical protuberances on their external surfaces that were probably created by the fusion of the smaller particles during the spray drying process (Fig. 2.2). Random TEM photographs of the CaF_2 nanoparticles were taken, and the sizes of 200 particles were estimated by magnification. The smallest particle size was found to be 15 nm and the largest was measured as 335 nm. The median particle size was 56 nm (Fig. 2.3).

The important characteristics of an ideal CaF_2 -based restorative nanocomposite include ion release, enhanced physical and mechanical properties (such as flexural strength, elastic modulus, fracture toughness, and water aging property), and antibacterial property.

2.6.1 Ion release

The relatively high fluoride release from the CaF_2 -based nanocomposites may be because of the smaller size, and hence, the high surface area of the nanoparticles. A few studies have also investigated the pH effect on fluoride release, as an acidic pH

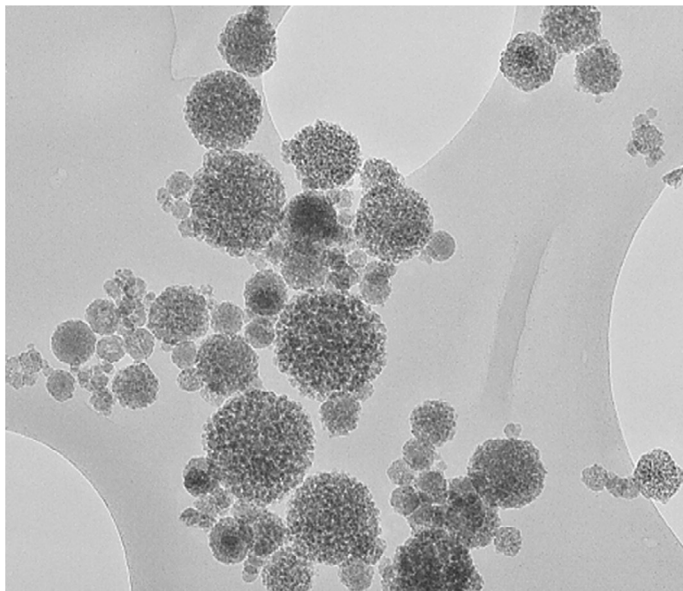


Fig. 2.1 TEM micrograph of CaF₂ nanoparticles.

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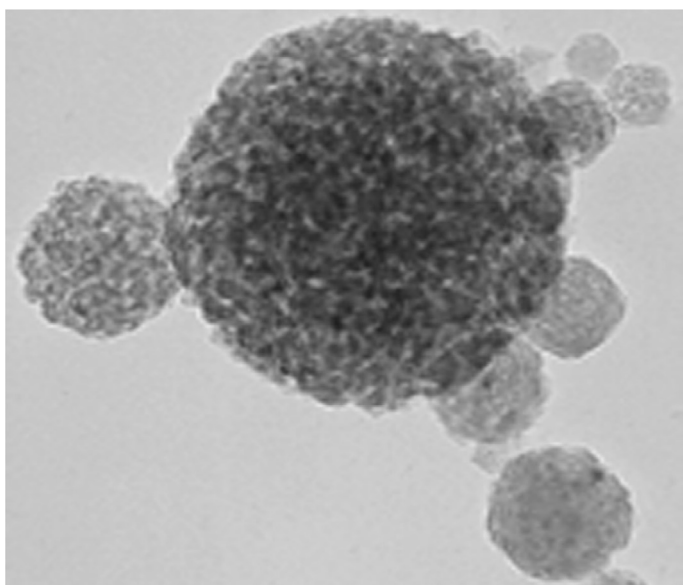


Fig. 2.2 CaF₂ nanoparticle at higher magnification.

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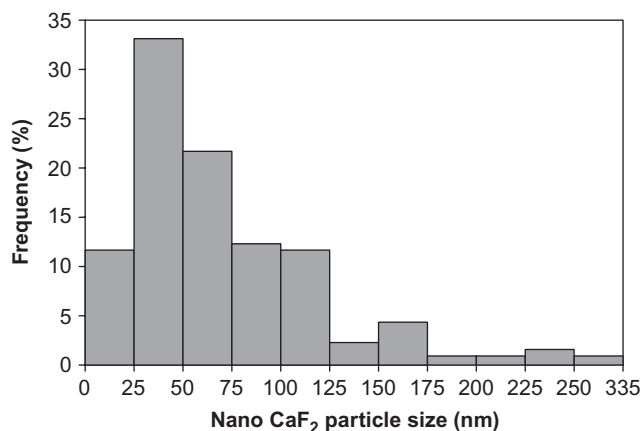


Fig. 2.3 Histogram of CaF₂ nanoparticle size distribution, obtained via measuring the sizes of 200 particles on TEM pictures. The particle size ranged from 15 to 335 nm, with a median (50th percentile) of 56 nm. BET surface area measurement yielded a specific surface area of 35.5 m²/g, and a calculated CaF₂ particle diameter of 53 nm.

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greater fluoride release is desired in order to combat the carious process. Calcium and $-\text{PO}_4$ ions are essential for the remineralization of the decayed tooth structure. In the study by Xu et al., the fluoride release from the CaF₂ based nanocomposite containing 25% whiskers, 20% CaF₂, and 20% DCPA was measured as 0.15 ± 0.03 mM/L on day 1; it increased to 0.68 ± 0.11 mM/L within 1 week; and 2.34 ± 0.26 mM/L within 10 weeks. The initial fluoride release rate reached 1.94 mg/(h cm²); but it decreased to a level of about 0.5 mg/(h cm²) after 500 h, and further decreased to about 0.29 mg/(h cm²) after 1680 h (10 weeks) (Fig. 2.4). The $-\text{PO}_4$ ion release increased rapidly from day 1 to about 2 weeks, after which, it plateaued by reaching a steady-state concentration of about 1.75 mM/L. The corresponding measured calcium ion release was low (at 0.03 mM/L) [32]. The main advantages of these CaF₂-based nanocomposites were the high release of ions that bring about the anticariogenic factor, even at lower filler levels, due to the high surface area of nanoparticles. Ion release for caries inhibition and stress bearing are the prime requisites for the fabrication of these nanocomposites.

2.6.2 Physical and mechanical properties

Dental nanocomposites impregnated with nanoparticles are characterized by superior hardness, flexural strength, modulus of elasticity, tensile strength, and a 50% reduction in filling shrinkage as compared with conventional composites. Incorporation of nanoparticles forms nonagglomerated discrete nanoparticles with a homogeneous distribution of constituents. The study by Xu et al. focused on the mechanical properties of the CaF₂-based dental nanocomposite, which resulted in the following revelations.

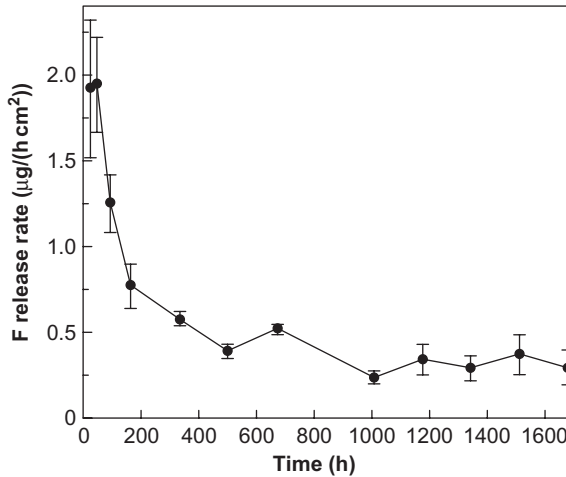


Fig. 2.4 Rate of fluoride release per hour per specimen surface area (mg/h cm^2) from nanocomposite containing mass fractions of 25% whiskers, 20% CaF_2 , and 20% DCPA. The initial release rate was nearly $2 \text{ mg/(h cm}^2\text{)}$. H.H.K. Xu, L. Jennifer, J.L. Moreau, L. Sun, L.C. Chow, Strength and fluoride release characteristics of a calcium fluoride based dental nanocomposite, *Biomaterials* 29 (2008) 4261–4267; Copyright © 2008 Elsevier Ltd.

In this study, flexural strength of the CaF_2 -based dental nanocomposite was measured [32]. It was found that decreasing the whisker content resulted in decreased strength of the CaF_2 -based dental nanocomposite. The flexural strength for the dental nanocomposite containing 65% whisker content (without incorporation of CaF_2 nanoparticles) was measured to be $145 \pm 9 \text{ MPa}$, which was significantly higher than $110 \pm 11 \text{ MPa}$ for the nanocomposite containing 30% CaF_2 nanoparticles and 35% whisker content. However, $93 \pm 5 \text{ MPa}$ flexural strength was measured for the nanocomposite containing 40% CaF_2 nanoparticles and 25% whisker content. The strengths of the CaF_2 -based dental nanocomposite did not differ much from the $108 \pm 19 \text{ MPa}$ of the commercial hybrid composite (Fig. 2.5A). The group of composite specimens containing 25% whiskers, 20% CaF_2 , and 20% DCPA exhibited a flexural strength of $100 \pm 7 \text{ MPa}$. The value is not much different from the $93 \pm 5 \text{ MPa}$ of the composite, with 25% whiskers and 40% CaF_2 . This denotes that as long as the composite contained the same amount of whiskers (25%), irrespective of the nanoparticles being either CaF_2 or DCPA, it did not significantly influence and alter the mechanical properties of the composite material. In a study by Weir et al., the measured flexural strengths were 94 MPa for nanocomposite containing 10% CaF_2 nanoparticles, 60 MPa for nanocomposite 20% CaF_2 nanoparticles, and 48 MPa for nanocomposite 30% CaF_2 nanoparticles at 2 years; much higher than the commercial composite control (15 MPa) [99]. The study reported by Xu et al. (2008) showed that dental nanocomposite containing 40% CaF_2 nanoparticles and 25% whisker content possessed much lower elastic modulus than that of the composite containing 65% whisker content (without incorporation of CaF_2 nanoparticles) (Fig. 2.5B) [32]. The CaF_2 -based dental nanocomposite exhibited modulus of

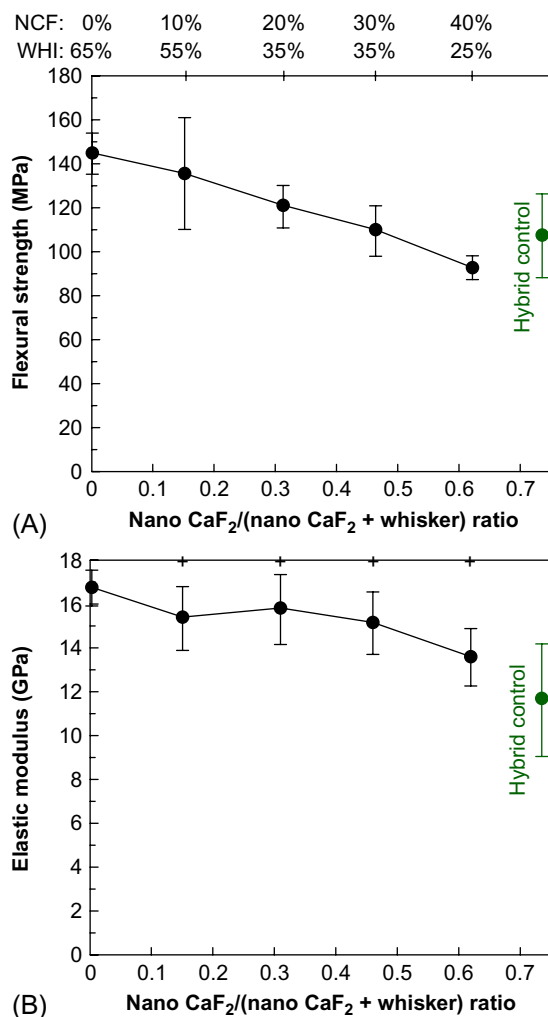


Fig. 2.5 (A) Flexural strength and (B) elastic modulus of dental resin composite containing CaF₂ nanoparticles. At the top, NCF denotes nanoparticles of CaF₂, and WHI denotes whisker content. The *x*-axis denotes the corresponding CaF₂/(CaF₂ + whisker) mass ratio, where “0” means all whiskers and no CaF₂.

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elasticity similar to that of the commercial hybrid composites. CaF₂ nanoparticles are being considered to increase fracture toughness, but further studies are still required in this aspect to prove the mechanism of toughening, and hence, their effects on the durability and longevity of the nanocomposite. In the study carried out by Weir et al., on CaF₂-based nanocomposites, where the long-term mechanical durability including

wear, thermal-cycling, and long-term water-aging behavior of the CaF_2 -based nanocomposite were investigated [99]. CaF_2 nanoparticles of diameter 53 nm and glass particles of 1.4 μm were used as fillers for the fabrication of four nanocomposites with the following filler contents:

- (i) 0% CaF_2 nanoparticles +65% glass
- (ii) 10% CaF_2 nanoparticles +55% glass
- (iii) 20% CaF_2 nanoparticles +45% glass, and
- (iv) 30% CaF_2 nanoparticles +35% glass

Weir et al. used three commercial composites as control. Specimens were treated with thermal-cycling between 5 and 60°C for 10^5 cycles, three-body wear for 4×10^5 cycles, and water-aging for 2 years [99]. Thermal-cycling exhibited that the CaF_2 nanocomposites possessed flexural strengths in the range of 100–150 MPa, which was five times higher than 20–30 MPa for RMGI. The wear for both the nanocomposite and the commercial control were found to be similar. Water-aging led to reduction of strength of all materials. Scanning electron microscopic results revealed air bubbles and cracks in RMGI, but the micrographs of CaF_2 -based nanocomposite and the composite control exhibited high density and a solid ultrastructure [96–98]. In a study by Cheng et al., chlorhexidine (CHX) was loaded to both CaPO_4 nanocomposites and CaF_2 nanocomposites, which showed that the addition of CHX reduced the strength of CaPO_4 nanocomposites and CaF_2 nanocomposites [46]. The CaF_2 nanocomposites also exhibited a similar 20% loss of strength. But, the strength of the nanocomposites containing CHX was almost like that of a commercial composite control without CHX. The strength of the CaF_2 nanocomposites consisting of CHX was twice that of a RMGI control.

2.6.3 Antibacterial property

Kulshrestha et al. showed that CaF_2 nanoparticles exhibited potent antibacterial activity against *Streptococcus mutans*, leading to approximately a 90% reduction of biofilm formation, decreased acid, and extracellular polysaccharide formation [100]. At low pH, fluoride and hydrogen ions react to form hydrofluoric acid (HF), which penetrates bacteria and inhibits enzymes (enolase and ATPase). Fluorides in very high concentrations, that is, 3040–5700 ppm, cause lysis of the bacterial cells. Fluoride ions adversely affect metabolism and adhesion of bacterial cells. The presence of CaF_2 nanoparticles is marked by decreased adhesion of microbes on the tooth surface, and a subsequent reduction in biofilm formation, followed by lessened carious process development. In a study by Cheng et al., novel nanocomposites containing amorphous CaPO_4 nanoparticles, CaF_2 nanoparticles, and CHX were fabricated to establish their effect on bacterial growth, biofilm formation, lactic acid production, and colony-forming units (CFU). CHX is a potent antimicrobial agent. This property of CHX was utilized in this study in reduction of biofilm formation and subsequent caries initiation and progression. The motives of study carried out by Cheng et al. were: (i) formation of nanocomposites consisting of amorphous CaPO_4 nanoparticles, CaF_2 nanoparticles and CHX, and (ii) inspection and documentation of the effects of

the formed nanocomposites on *S. mutans* biofilm formation and lactic acid production for the first time [46]. Four nanocomposites were fabricated with fillers of: CaPO_4 nanoparticles, CaPO_4 nanoparticles and 10% CHX, CaF_2 nanoparticles and CaF_2 nanoparticles and 10% CHX. A commercial composite with fluoride release, a composite without fluoride release, and a RMGI were also investigated. Adding CHX to the amorphous CaPO_4 and CaF_2 nanocomposites promoted the antimicrobial property. Nanocomposites containing CHX decreased acid production and biofilm formation compared with the commercial composite. In addition, CFU of nanocomposites with CHX were ordered to a lesser magnitude as compared with the commercial composite. These novel nanocomposites successfully released phosphate and fluoride ions to promote remineralization and resist acid attacks, respectively. These also decreased biofilm formation and lactic acid production. The CaF_2 -based nanocomposites were found antimicrobial, mechanically strong, and chemically stable materials with anticariogenic properties, which can be a prospective dental material for restoration of decayed tooth structure. As compared with commercial control composites, nanoparticles of amorphous CaPO_4 were found to possess minimum antibacterial property; whereas CaF_2 nanoparticles were antibacterial to some extent. Addition of CHX into the amorphous CaPO_4 and CaF_2 -based nanocomposites led to the enhancement of the microbial property. Uniquely, the CaF_2 -based nanocomposites containing CHX had a higher pH than that of CaPO_4 based nanocomposites containing CHX, which can be attributed by the fact due to the release of fluoride ions that helped in decreasing the acid production of the bacteria by preventing metabolic pathways like the fermentation pathway for lactic acid production. Compared with the commercial composite, where pH reduced to 4.2, CHX containing nanocomposite maintained *S. mutans* culture media at a pH 6.5, which prevented demineralization of tooth structure. Ion release facilitated remineralization and formation of fluoroapatite for anticariogenicity. Hence, these nanocomposites caused inhibition of biofilm formation and subsequent prevention of dental caries. Because CHX is a very potent antimicrobial agent, the additional fluoride release from CaF_2 -based nanocomposites containing CHX should be beneficial in further decreasing lactic acid production, which is required for caries initiation, hence successfully jeopardizing the carious process. Further studies are being carried out to emphasize the antimicrobial and anticariogenic abilities of the CaF_2 -based nanocomposites.

2.7 Conclusion

The development of CaF_2 -based dental nanocomposites is a recent discovery, which has gained much attention in dentistry. In the past few years, CaF_2 -based dental nanocomposites have been designed and evaluated by various research groups. These CaF_2 -based dental nanocomposites were found to be competent, having both superior mechanical, as well as fluoride releasing properties. Because the CaF_2 -based nanocomposites are able to release fluoride ions along with greater mechanical properties than the commercial composites, these can be ideal restorative materials with a good

long-term prognosis. The strong mechanical properties and anticariogenic potential of CaF₂-based dental nanocomposites can be utilized in conservative and esthetic dentistry. CaF₂-based nanocomposites are promising in the field of dentistry due to their stress-bearing ability and cariostatic properties. Hence, CaF₂-based nanocomposites may undoubtedly be considered as a boon for restorative dentistry.

References

- [1] R.P. Feynman, There's plenty of room at the bottom, *Eng. Sci.* 23 (1960) 22–36.
- [2] R.P. Feynman, There's plenty of room at the bottom (data storage), *J. Microelectromech. Syst.* 1 (1992) 60–66.
- [3] N. Taniguchi, On the basic concept of nano-technology, in: *Proc. Int. Conf. Prod., British Society of Precision Engineering*, London, 1974.
- [4] K.E. Drexler, *Engines of Creation: The Coming Era of Nanotechnology*, Doubleday, 1986.
- [5] K.E. Drexler, *Nanosystems: Molecular Machinery, Manufacturing, and Computation*, John Wiley & Sons, Inc., NY, USA, 1992.
- [6] K.K. Jain, *The Handbook of Nanomedicine*, Humana Press, Totowa, NJ, 2008.
- [7] A.K. Nayak, A.K. Dhara, Nanotechnology in drug delivery applications, *Arch. Appl. Sci. Res.* 2 (2010) 284–293.
- [8] D. Pal, A.K. Nayak, Nanotechnology for targeted delivery in cancer therapeutics, *Int. J. Pharm. Sci. Rev. Res.* 1 (2010) 1–7.
- [9] A.C. Balazs, T. Emrick, T.P. Russell, Nanoparticle polymer composites: where two small worlds meet, *Science* 314 (2006) 1107–1110.
- [10] S. Beg, M. Rizwan, M.S. Hasnain, A.M. Sheikh, K. Anwer, K. Kohli, Advancement in carbon nanotubes: basics, biomedical applications and toxicity, *J. Pharm. Pharmacol.* 63 (2011) 141–163.
- [11] J. Malakar, A. Ghosh, A. Basu, A.K. Nayak, Nanotechnology: a promising carrier for intracellular drug delivery system, *Int. Res. J. Pharm.* 3 (2012) 36–40.
- [12] J. Malakar, A. Basu, A.K. Nayak, Candesartan cilexetil microemulsions for transdermal delivery: formulation, *in-vitro* skin permeation and stability assessment, *Curr. Drug Deliv.* 11 (2014) 313–321.
- [13] S. Jana, N. Maji, A.K. Nayak, K.K. Sen, S.K. Basu, Development of chitosan-based nanoparticles through inter-polymeric complexation for oral drug delivery, *Carbohydr. Polym.* 98 (2013) 870–876.
- [14] A.K. Nayak, D. Pal, M.S. Hasnain, Development, optimization and in vitro-in vivo evaluation of pioglitazone-loaded jackfruit seed starch-alginate beads, *Curr. Drug Deliv.* 10 (5) (2013) 608–619.
- [15] P. Sinha, U. Ubaidulla, A.K. Nayak, M.S. Hasnain, B. Rama, Alginate-okra gum blend beads of diclofenac sodium from aqueous template using ZnSO₄ as a cross-linker. *Int. J. Biol. Macromol.* 79 (2015) 555–563, <https://doi.org/10.1016/j.ijbiomac.2015.04.067>.
- [16] M.S. Hasnain, P. Poonam Rishishwar, S. Sadath Ali, Use of cashew bark exudate gum in the preparation of 4% lidocaine HCL topical gels, *Int. J. Pharm. Pharm. Sci.* 9 (8) (2017) 146–150.
- [17] M.S. Hasnain, P. Poonam Rishishwar, S. Sadath Ali, Floating-bioadhesive matrix tablets of hydralazine HCL made of cashew gum and HPMC K4M, *Int. J. Pharm. Pharm. Sci.* 9 (7) (2017) 124–129.

- [18] A.K. Nayak, S. Khatua, M.S. Hasnain, K.K. Sen, Development of diclofenac sodium-loaded alginate-PVP K 30 microbeads using central composite design, *Daru* 19 (2011) 5.
- [19] A.K. Nayak, D. Pal, J. Pradhan, M.S. Hasnain, Fenugreek seed mucilage-alginate muco-adhesive of metformin HCl: design, optimization and evaluation, *Int. J. Biol. Macromol.* 54 (2013) 144–154.
- [20] P.R. Guru, H. Bera, M.P. Das, M.S. Hasnain, A.K. Nayak, Aceclofenac-loaded *Plantago ovata* F. husk mucilage-Zn²⁺-pectinate controlled-release matrices. *Starch* (2017) <https://doi.org/10.1002/star.201700136>.
- [21] A.K. Nayak, J. Malakar, D. Pal, M.S. Hasnain, S. Beg, Soluble starch-blended Ca²⁺-Zn²⁺-alginate composites-based microparticles of aceclofenac: formulation development and in vitro characterization. *Futur. J. Pharm. Sci.* (2017) <https://doi.org/10.1016/j.fjps.2017.10.001>.
- [22] A.K. Nayak, S. Kalia, M.S. Hasnain, Optimization of aceclofenac-loaded pectinate-poly (vinyl pyrrolidone) beads by response surface methodology, *Int. J. Biol. Macromol.* 62 (2013) 194–202.
- [23] N.A. Abdelwahab, N. Shukry, Synthesis, characterization and antimicrobial properties of grafted sugarcane bagasse/silver nanocomposites, *Carbohydr. Polym.* 115 (2015) 276–284.
- [24] B. Ben-Nissan, I. Macha, S. Cazalbou, A.H. Choi, Calcium phosphate nanocoatings and nanocomposites, part 2: thin films for slow drug delivery and osteomyelitis, *Nanomedicine* 11 (2016) 531–544.
- [25] M.S. Hasnain, A.K. Nayak, M. Singh, M. Tabish, M.T. Ansari, T.J. Ara, Alginate-based bipolymeric-nanobioceramic composite matrices for sustained drug release, *Int. J. Biol. Macromol.* 83 (2016) 71–77.
- [26] H. Ullah, F. Wahid, H.A. Santos, T. Khan, Advances in biomedical and pharmaceutical applications of functional bacterial cellulose-based nanocomposites, *Carbohydr. Polym.* 150 (2016) 330–352.
- [27] A. Bhowmick, N. Pramanik, P. Jana, T. Mitra, A. Gnanamani, M. Das, P.P. Kundu, Development of bone-like zirconium oxide nanoceramic modified chitosan based porous nanocomposites for biomedical application, *Int. J. Biol. Macromol.* 95 (2017) 348–356.
- [28] S. Chen, S. Cui, J. Hu, Y. Zhou, Y. Liu, Pectinate nanofiber mat with high absorbency and antibacterial activity: a potential superior wound dressing to alginate and chitosan nanofiber mats, *Carbohydr. Polym.* 174 (2017) 591–600.
- [29] B. Das, S.O. Sen, R. Maji, A.K. Nayak, K.K. Sen, Transfersomal gel for transdermal delivery of risperidone, *J. Drug Delivery Sci. Technol.* 38 (2017) 59–71.
- [30] S.S. Bari, S. Mishra, Effect of calcium sulphate nanorods on mechanical properties of chitosan-hydroxyethyl methacrylate (HEMA) copolymer nanocomposites, *Carbohydr. Polym.* 157 (2017) 409–418.
- [31] B.S. Harrison, A. Atala, Carbon nanotube applications for tissue engineering, *Biomaterials* 28 (2007) 344–353.
- [32] H.H.K. Xu, J.L. Moreau, L. Sun, L.C. Chow, Strength and fluoride release characteristics of a calcium fluoride based dental nanocomposite, *Biomaterials* 29 (2008) 4261–4267.
- [33] M.S. Hasnain, A.K. Nayak, R. Singh, F. Ahmad, Emerging trends of natural-based polymeric systems for drug delivery in tissue engineering applications, *Sci. J. UBU* 1 (2010) 1–13.
- [34] P.T.S. Kumar, S. Abhilash, K. Manzoor, S.V. Nair, H. Tamura, R. Jayakumar, Preparation and characterization of novel b-chitin/nanosilver composite scaffolds for wound dressing applications, *Carbohydr. Polym.* 80 (2010) 761–767.

- [35] R. Kanaparthi, A. Kanaparthi, The changing face of dentistry: nanotechnology, *Int. J. Nanomedicine* 6 (2011) 2799.
- [36] J. Malakar, S.O. Sen, A.K. Nayak, K.K. Sen, Formulation, optimization and evaluation of transferosomal gel for transdermal insulin, *Saudi Pharm. J.* 20 (2012) 355–363.
- [37] S. Jana, S. Manna, A.K. Nayak, K.K. Sen, S.K. Basu, Carbopol gel containing chitosan-egg albumin nanoparticles for transdermal aceclofenac delivery, *Colloids Surf. B: Biointerfaces* 114 (2014) 36–44.
- [38] A.S. Montaser, A.M. Abdel-Mohsen, M.A. Ramadan, A.A. Sleem, N.M. Sahffie, J. Jancar, A. Hebeish, Preparation and characterization of alginate/silver/nicotinamide nanocomposites for treating diabetic wounds, *Int. J. Biol. Macromol.* 92 (2016) 739–747.
- [39] R.A. Freitas, Nanodentistry, *J. Am. Dent. Assoc.* 131 (2000) 1559–1565.
- [40] R.A. Freitas, Nanotechnology, nanomedicine and nanosurgery, *Int. J. Surg.* 3 (2005) 243–246.
- [41] K.R. Saravana, R. Vijayalakshmi, Nanotechnology in dentistry, *Indian J. Dent. Res.* 17 (2006) 62–65.
- [42] Y. Xia, F. Zhang, H. Xie, N. Gu, Nanoparticle-reinforced resinbased dental composites, *J. Dent.* 36 (2008) 450–455.
- [43] A.P. Tomsia, M.E. Launey, J.S. Lee, M.H. Mankani, U.G. Wegst, E. Saiz, Nanotechnology approaches for better dental implants, *Int. J. Oral Maxillofac. Implants* 26 (2011) 25–49.
- [44] M.-H. Chen, Update on dental nanocomposites, *J. Dent. Res.* 89 (2010) 549–560.
- [45] S.E. Langhorst, J.N.R. O'Donnell, D. Skrtic, *In vitro* remineralization of enamel by polymeric amorphous calcium phosphate composite: quantitative microradiographic study, *Dent. Mater.* 25 (2009) 884–891.
- [46] L. Cheng, M.D. Weir, H.H. Xu, A.M. Kraigsley, N.J. Lin, S. Lin-Gibson, X. Zhou, Antibacterial and physical properties of calcium–phosphate and calcium–fluoride nanocomposites with chlorhexidine, *Dent. Mater.* 28 (2012) 573–583.
- [47] A.K. Nayak, Hydroxyapatite synthesis methodologies: an overview, *Int. J. ChemTech Res.* 2 (2010) 903–907.
- [48] A.H. Choi, B. Ben-Nissan, Applications of hydroxyapatite nanocoatings and nanocomposite coatings in dentistry, *JSM Dent. Surg.* 1 (2016) 1002.
- [49] A. Polini, H. Bai, A.P. Tomsia, Dental applications of nanostructured bioactive glass and its composites, *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* 5 (2013) 399–410.
- [50] M. Aukomska-Szymanska, J. Kleczewska, J. Nowak, M. Prylinski, A. Szczesio, M. Podlewska, J. Sokolowski, B. Aapinska, Mechanical properties of calcium fluoride-based composite materials, *Biomed. Res. Int.* (2016) 2752506. 8 pages.
- [51] M. Saxena, A. Pappu, A. Sharma, R. Haque, S. Wankhede, Composite materials from natural resources: recent trends and future potentials, in: P. Tesinova (Ed.), *Advances in Composite Materials-Analysis of Natural and Man-made Materials*, InTech, 2011, pp. 122–162.
- [52] P.M. Ajayan, *Nanocomposite Science and Technology*, Wiley-VCH Verlag, Weinheim, 2000.
- [53] E.T. Thostenson, C. Li, T.W. Chou, Nanocomposites in context, *Compos. Sci. Technol.* 65 (2005) 491–516.
- [54] D.R. Paul, L.M. Robeson, Polymer nanotechnology: nanocomposites, *Polymer* 49 (2008) 3187–3204.
- [55] J. Jordan, K.I. Jacob, R. Tannenbaum, M.A. Sharaf, I. Jasiuk, Experimental trends in polymer nanocomposites—a review, *Mater. Sci. Eng. A* 393 (2005) 1–11.
- [56] I.-Y. Jeon, J.-B. Baek, Nanocomposites derived from polymers and inorganic nanoparticles, *Materials* 3 (2010) 3654–3674.

- [57] N. Raman, S. Sudharsan, K. Pothiraj, Synthesis and structural reactivity of inorganic–organic hybrid nanocomposites—a review, *J. Saudi Chem. Soc.* 16 (2012) 339–352.
- [58] M.S. Soh, A. Sellinger, A.U.J. Yap, Dental nanocomposites, *Curr. Nanosci.* 2 (2006) 373–381.
- [59] P.H.C. Camargo, K.G. Satyanarayana, F. Wypych, Nanocomposites: synthesis, structure, properties and new application opportunities, *Mater. Res.* 12 (2009) 1–39.
- [60] H.W. Kim, H.E. Kim, V. Salih, Stimulation of osteoblast responses to biomimetic nanocomposites of gelatin-hydroxyapatite for tissue engineering scaffolds, *Biomaterials* 26 (2005) 5221–5230.
- [61] C.J. Grande, F.G. Torres, C.M. Gomez, M.C. Bañó, Nanocomposites of bacterial cellulose/hydroxyapatite for biomedical applications, *Acta Biomater.* 5 (2009) 1605–1615.
- [62] B.A. Allo, D.O. Costa, S.J. Dixon, K. Mequanint, A.S. Rizkalla, Bioactive and biodegradable nanocomposites and hybrid biomaterials for bone regeneration, *J. Funct. Biomater.* 3 (2012) 432–463.
- [63] A.K. Gaharwar, N.A. Peppas, A. Khademhosseini, Nanocomposite hydrogels for biomedical applications, *Biotechnol. Bioeng.* 111 (2014) 441–453.
- [64] Y. Zheng, J. Monty, R.J. Linhardt, Polysaccharide-based nanocomposites and their applications, *Carbohydr. Res.* 405 (2015) 23–32.
- [65] R. Zafar, K.M. Zia, S. Tabasum, F. Jabeen, A. Noreen, M. Zuber, Polysaccharide based bionanocomposites, properties and applications: a review, *Int. J. Biol. Macromol.* 92 (2016) 1012–1024.
- [66] S. Jahanizadeh, F. Yazdian, A. Marjani, M. Omid, H. Rashedi, Curcumin-loaded chitosan/carboxymethyl starch/montmorillonite bio-nanocomposites for reduction of dental bacterial biofilm formation, *Int. J. Biol. Macromol.* 105 (2017) 757–763.
- [67] F. Panahi, S.M. Rabiee, R. Reza Shidpour, Synergic effect of chitosan and dicalcium phosphate on tricalcium silicate-based nanocomposites for root-end dental application, *Mater. Sci. Eng. C* 80 (2017) 631–641.
- [68] X. Liu, K. Zhao, T. Gong, J. Song, C. Bao, E. Luo, J. Weng, S. Zhou, Delivery of growth factors using a smart porous nanocomposite scaffold to repair a mandibular bone defect, *Biomacromolecules* 15 (2014) 1019–1030.
- [69] S. Nath, B. Basu, M. Mohanty, P.V. Mohanan, *In vivo* response of novel hydroxyapatite-mullite composites: results up to 12 weeks of implantation, *J. Biomed. Mater. Res. B.* 90B (2009) 547–557.
- [70] M. Peter, N.S. Binulal, S. Soumya, S.V. Nair, T. Furuike, H. Tamura, R. Jayakumar, Nanocomposite scaffolds of bioactive glass ceramic nanoparticles disseminated chitosan matrix for tissue engineering applications, *Carbohydr. Polym.* 79 (2010) 284–289.
- [71] S. Bala Subramanian, A.P. Francis, T. Devasena, Chitosan-starch nanocomposite particles as a drug carrier for the delivery of bis-desmethoxy curcumin, analog, *Carbohydr. Polym.* 114 (2014) 170–178.
- [72] R.I. Illiescu, E. Andronescu, C.D. Ghitulica, G. Voicu, A. Ficai, M. Hotetu, Montmorillonite-alginate nanocomposite as a drug delivery system-incorporation and *in vitro* release of irinotecan, *Int. J. Pharm.* 463 (2014) 184–192.
- [73] J. Zhang, Q. Wang, A. Wang, *In situ* generation of sodium alginate/hydroxyapatite nanocomposite beads as drug-controlled release matrices, *Acta Biomater.* 6 (2010) 445–454.
- [74] A.K. Nayak, K.K. Sen, Hydroxyapatite-ciprofloxacin implantable minipellets for bone delivery: preparation, characterization, *in vitro* drug adsorption and dissolution studies, *Int. J. Drug Dev. Res.* 1 (2009) 47–59.

- [75] A.K. Nayak, A. Bhattacharya, K.K. Sen, Hydroxyapatite-antibiotic implantable minipellets for bacterial bone infections using precipitation technique: preparation, characterization and *in-vitro* antibiotic release studies, *J. Pharm. Res.* 3 (2010) 53–59.
- [76] A.K. Nayak, A. Bhattacharyya, K.K. Sen, *In vivo* ciprofloxacin release from hydroxyapatite-based bone implants in rabbit tibia: a preliminary study, *ISRN Orthop.* 2011 (2011) 1–4.
- [77] A.K. Nayak, B. Laha, K.K. Sen, Development of hydroxyapatite-ciprofloxacin bone-implants using “Quality by Design”, *Acta Pharm.* 6 (2011) 25–36.
- [78] A.K. Nayak, M.S. Hasnain, J. Malakar, Development and optimization of hydroxyapatite-ofloxacin implants for possible bone-implantable delivery in osteomyelitis treatment, *Curr. Drug Deliv.* 10 (2013) 241–250.
- [79] G.A.X. Acasigua, G.M. Olyveira, L.M.M. Costa, D.I. Braghirolli, A. Fossati, A.C.M. Carlos Guastaldi, et al., Novel chemically modified bacterial cellulose nanocomposite as potential biomaterial for stem cell therapy applications, *Curr. Stem Cell Res. Ther.* 9 (2014) 117–123.
- [80] H. Ghanbari, D. Radenkovic, S.M. Marashi, S. Parsno, N. Roohpour, G. Burriesci, A.M. Seifalian, Novel heart valve prosthesis with self-endothelialization potential made of modified polyhedral oligomeric silsesquioxane-nanocomposite material, *Biointerphases* 11 (2016) 029801.
- [81] H. Mohammadi, D. Boughner, L.E. Millon, W.K. Wan, Design and simulation of a poly(vinyl alcohol)-bacterial cellulose nanocomposite mechanical aortic heart valve prosthesis, *Proc. Inst. Mech. Eng. H* 223 (2009) 697–711.
- [82] E.E. Brown, D. Hu, N. Abu Lail, X. Zhang, Potential of nanocrystalline cellulose-fibrin nanocomposites for artificial vascular graft applications, *Biomacromolecules* 14 (2013) 1063–1071.
- [83] M. Sneha, N.M. Sundaram, Preparation and characterization of an iron oxide-hydroxyapatite nanocomposite for potential bone cancer therapy, *Int. J. Nanomedicine* 2015 (10) (2015) 99–1106.
- [84] D. Archana, B.K. Singh, J. Dutta, P.K. Dutta, *In vivo* evaluation of chitosan–PVP–titanium dioxide nanocomposite as wound dressing material, *Carbohydr. Polym.* 95 (2013) 530–539.
- [85] A. Khalid, R. Khan, M.R. Ul-Islam, T. Khan, F. Wahid, Bacterial cellulose–zinc oxide nanocomposites as a novel dressing system for burn wounds, *Carbohydr. Polym.* 164 (2017) 214–221.
- [86] I. Malagurski, S. Levic, M. Pantic, D. Matijasevic, M. Mitric, V. Pavlovic, S. Dimitrijevic-Brankovic, Synthesis and antimicrobial properties of Zn-mineralized alginate nanocomposites, *Carbohydr. Polym.* 165 (2017) 313–321.
- [87] N. Ruecha, R. Rangkupan, N. Rodthongkum, O. Chailapakul, Novel paper-based cholesterol biosensor using graphene/polyvinylpyrrolidone/polyaniline nanocomposite, *Biosens. Bioelectron.* 52 (2014) 13–19.
- [88] M.P. Ferraz, A.Y. Mateus, J.C. Sousa, F.J. Monteiro, Nanohydroxyapatite microspheres as delivery system for antibiotics: release kinetics, antimicrobial activity, and interaction with osteoblasts, *J. Biomed. Mater. Res. A* 81A (2007) 994–1004.
- [89] P. Patnaik, *Handbook of Inorganic Chemicals*, McGraw-Hill, USA, 2001.
- [90] A.F. Holleman, E. Wiberg, *Inorganic Chemistry*, Academic Press, San Diego, 2001.
- [91] L.M. Tenuta, R.V. Cerezetti, A.A. Del Bel Cury, C.P. Tabchoury, J.A. Cury, Fluoride release from CaF_2 and enamel demineralization, *J. Dent. Res.* 87 (2008) 1032–1036.
- [92] G. Rölla, E. Saxegaard, Critical evaluation of the fluorides with emphasis on the role of calcium fluoride in caries inhibition, *J. Dent. Res.* 69 (1990) 780–785.

- [93] D.C. Sarrett, Clinical challenges and the relevance of materials testing for posterior composite restorations, *Dent. Mater.* 21 (2005) 9–20.
- [94] C.Y. Hsu, K.J. Donly, D.R. Drake, J.S. Wefel, Effects of aged fluoride-containing restorative materials on recurrent root caries, *J. Dent. Res.* 77 (1998) 418–425.
- [95] A. Wiegand, W. Buchalla, T. Attin, Review on fluoride-releasing restorative materials—fluoride release and uptake characteristics, antibacterial activity and influence on caries formation, *Dent. Mater.* 23 (2007) 343–362.
- [96] H.H.K. Xu, F.C. Eichmiller, D.T. Smith, G.E. Schumacher, A.A. Giuseppetti, J.M. Antonucci, Effect of thermal cycling on whisker-reinforced dental resin composites, *J. Mater. Sci. Mater. Med.* 13 (2002) 875–883.
- [97] H.H.K. Xu, Long-term water-aging of whisker-reinforced polymer-matrix composites, *J. Dent. Res.* 82 (2003) 48–52.
- [98] H.H.K. Xu, J.B. Quinn, A.A. Giuseppetti, Wear and mechanical properties of nano-silica-fused whisker composites, *J. Dent. Res.* 83 (2004) 930–935.
- [99] M.D. Weir, J.L. Moreau, E.D. Levine, H.D. Strassler, L.C. Chow, H.H.K. Xu, Nanocomposite containing CaF_2 nanoparticles: thermal cycling, wear and long-term water-aging, *Dent. Mater.* 28 (2012) 642–652.
- [100] S. Kulshrestha, S. Khan, S. Hasan, M.E. Khan, L. Misba, A.U. Khan, Calcium fluoride nanoparticles induced suppression of *Streptococcus mutans* biofilm: an *in vitro* and *in vivo* approach, *Appl. Microbiol. Biotechnol.* 100 (2016) 1901–1914.