

# Nanocomposite restorative materials for dental caries management

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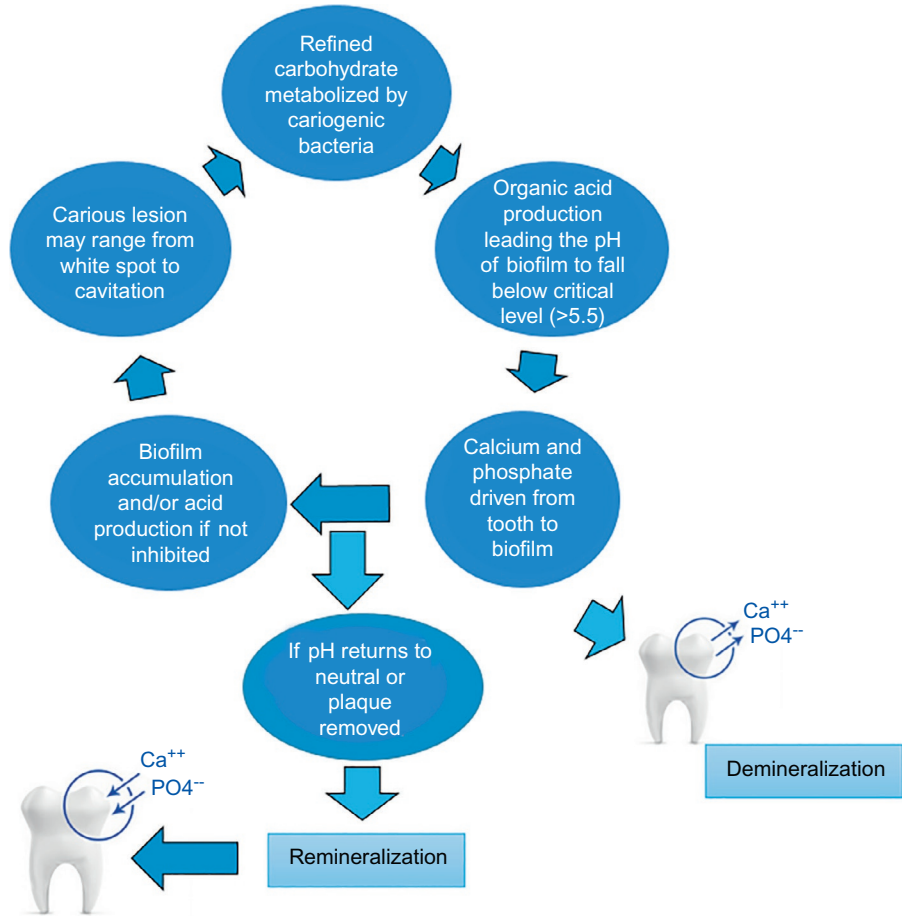
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## 9.1 Nanotechnology as an innovative concept

Nanotechnology is one of the most exciting and popular areas of current research, and has been developed in multiple disciplines. Nanotechnology facilitates designing, functioning, and performance of products on dimensions of  $<100$  nm [1]. At nanoscale, physical, chemical, and biological properties of materials are different from those found at an individual atomic/molecular level [2]. Owing to their unique properties, nanomaterials have been used in various health care applications, such as molecular diagnostics, drug delivery, gene delivery, and imaging tools [3]. The innovative concept of nanotechnology has been applied in dentistry to develop dental materials with better properties, anticaries potential, and as mineralization enhancers. One area of dentistry where nanotechnology has been extensively explored is the addition of nanoparticles in composites and ceramics. The addition of nanoparticles in these materials improves the aesthetics, wear properties, and strength tremendously.

## 9.2 Mechanism of dental caries

Dental caries are one of the most prevalent diseases affecting tooth structures. The attributable tooth destruction results from a complex interaction of cariogenic oral bacteria (such as *Streptococcus mutans*, *Streptococcus sobrinus*, and *Lactobacillus* present in the form of oral biofilms) with fermentable dietary carbohydrates on the tooth surface over time [4, 5]. Thus, caries result from a dynamic process of attack (demineralization) and restitution (remineralization) of the tooth structure with the balance tilting more toward demineralization (Fig. 9.1). Cariogenic bacteria in the biofilm metabolizes refined carbohydrates and produces an organic acid by-product. These organic acids, when present in the biofilm ecosystem for extended periods, can lower the pH to below a critical level (5.5 for enamel and 6.2 for dentin). The lower pH drives calcium and phosphate from the tooth to biofilm, causing tooth demineralization. In the remineralization process, calcium and phosphate lost by the enamel is deposited into the tooth from dental plaque fluid, or by direct action of salivary calcium and phosphate, soon after the biofilm is removed [6]. If biofilm accumulation and/or acid production are not



**Fig. 9.1** Demineralization and remineralization cycle.

inhibited, enamel mineral loss will continue by repeated events of mineral dissolution (demineralization), eventually exceeding the capacity of oral fluids to repair mineral loss evidenced clinically as carious lesions or a cavity [7].

Dental caries can therefore be controlled through (i) limiting the growth of caries-related bacteria and altering its metabolism, (ii) increasing biofilm pH, or (iii) reduction of demineralization and/or increase of remineralization of dental hard tissues.

### 9.3 Nanocomposites in restorative dentistry

Composite resins are increasingly used nowadays for restoring dental cavities because of their ability to imitate the color and transparency of surrounding teeth. It is composed of four major components: organic resin matrix, filler (inorganic) particles,

a coupling agent (silane), and the initiator-accelerator system for polymerization [8]. Despite the aesthetic improvement of resin composite relative to amalgam, certain drawbacks, such as polymerization shrinkage, microleakage, secondary caries, low strength, low fracture toughness, and wear still remain. Composite resins that incorporate nanoparticles (size  $\leq 100$  nm) and nanoclusters with a broad particle distribution provide potentially useful attributes, such as small particle size, high surface area, and optical properties of the resulting composite. Nanocomposites have better finishing, polishing, and shade matching capabilities; as well as flexural strength and hardness, compared with conventional composites. Nanoparticles have great potential to control the formation of biofilms within the oral cavity, as a function of their biocidal, antiadhesive, and delivery capabilities.

## 9.4 Nanocomposites and their role in dental caries prevention

Nanoparticles of silver, zinc oxide, quaternary ammonium polyethylenimine, calcium phosphate, calcium fluoride, titanium oxide, nanohydroxyapatite and/or nanofluorohydroxyapatite have been incorporated into dental composites [9] or adhesives [10] to combat dental caries through several mechanisms (Table 9.1).

### 9.4.1 *Antibacterial nanocomposites (containing nanoparticles of silver, zinc oxide, quaternary ammonium polyethylenimine)*

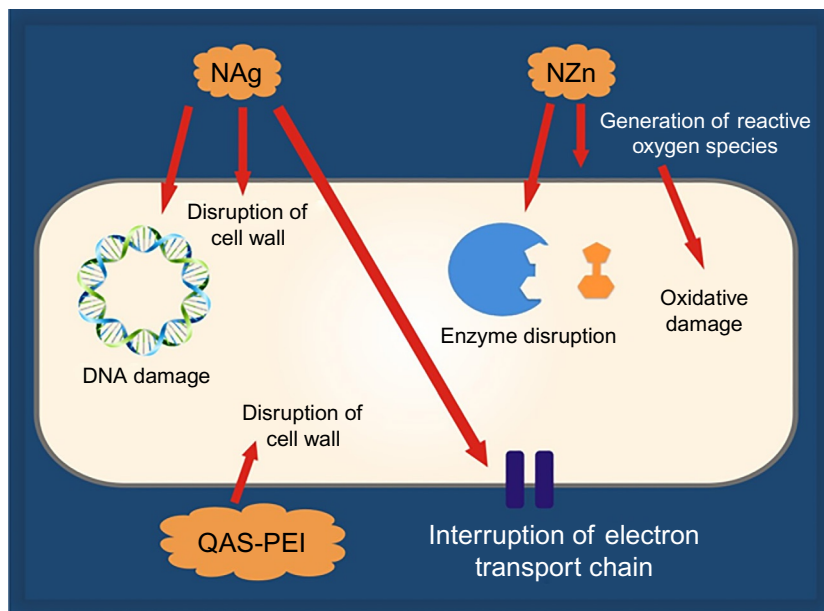
#### 9.4.1.1 *Silver nanoparticles (N<sub>Ag</sub>)*

Silver has antibacterial, antifungal, and antiviral properties [11]. The exact mechanism by which silver nanoparticles exert antimicrobial effect is not clearly known, and is a debated topic. There are various theories proposed on its action on microbes to cause the microbicidal effect. Silver nanoparticles interact with the peptidoglycan cell wall and the plasma membrane. They anchor to the cell wall of bacteria to penetrate it, causing increased permeability of the cell membrane, and ultimately cell death. Generation of free radicals by the silver nanoparticles is considered to be another mechanism by which cell death occurs. These free radicals, when in contact with the bacteria, have the ability to damage the cell membrane and make it porous, leading to death of bacterial cells [12]. Another possible mechanism is that there can be a release of silver ions by the nanoparticles that interact with bacterial DNA, and prevent its replication by interacting with the exposed sulfhydryl groups in bacterial proteins, especially with the enzymes involved in the electron transport chain [13] (Fig. 9.2). Silver-containing silica particles were used as fillers to synthesize antibacterial dental composites [14, 15]. Nanoparticles of silver have a high surface-area-to-mass ratio; hence, a small amount of N<sub>Ag</sub> was sufficient for the composite to be strongly antibacterial. A small amount of N<sub>Ag</sub> did not compromise the color, aesthetics, or mechanical properties of the composite [16]. Studies have

**Table 9.1 Nanoparticles and their possible mechanism of action**

|                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Silver nanoparticles (NAg)<br>(Incorporated in either composite resin; dental primer; dental adhesive) | <p><i>Antimicrobial</i></p> <ul style="list-style-type: none"> <li>• Bactericidal effect by interactions with the peptidoglycan cell wall and the plasma membrane.</li> <li>• Generation of free radicals by the nanoparticles of silver, making cell membrane porous, and ultimately leading to death of the bacterial cell.</li> <li>• Prevents bacterial DNA replication by interacting with the exposed sulfhydryl groups in bacterial proteins, especially with the enzymes involved in the electron transport chain</li> </ul> |
| Zinc oxide nanoparticles (NZn)<br>(Incorporated in composite resin)                                    | <p><i>Antimicrobial</i></p> <ul style="list-style-type: none"> <li>• Antibacterial mechanism of NZn is due to release of active oxygen species such as <math>O_2</math>, <math>H_2O_2</math>, and <math>OH^-</math> that inhibit bacterial growth.</li> <li>• Inhibits the active transport and metabolism of sugars, as well as disrupting enzyme systems by displacing magnesium ions essential for enzymatic activity of the of dental biofilms</li> </ul>                                                                        |
| Quaternary ammonium polyethylenimine nanoparticles.<br>(Incorporated in Composite resin & adhesives)   | <p><i>Antimicrobial</i></p> <ul style="list-style-type: none"> <li>• QAS materials appear to cause bacterial lysis by cationic binding and electrostatic interaction between nanoparticles of QA-PEI to the cell membrane of bacteria, causing cytoplasmic leakage</li> </ul>                                                                                                                                                                                                                                                        |
| Calcium phosphate nanoparticles (NACP)<br>(Incorporated in Composite resin, Dental adhesive)           | <p><i>Remineralizing</i></p> <ul style="list-style-type: none"> <li>• NACP greatly increases calcium and phosphate ion release at a cariogenic low pH, inhibiting dental caries.</li> </ul>                                                                                                                                                                                                                                                                                                                                          |
| Calcium fluoride nanoparticles.<br>(Incorporated in Composite resin)                                   | <p><i>Remineralizing</i></p> <ul style="list-style-type: none"> <li>• Enhances tooth remineralization.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Nanohydroxyapatite and nanofluorohydroxyapatite                                                        | <p><i>Remineralizing</i></p> <ul style="list-style-type: none"> <li>• Promotes remineralization of caries lesions to a depth of 20–40 <math>\mu m</math>. Carbonate hydroxyl apatite nanoparticles were also effective in repairing micrometer-sized defects in tooth surfaces in vitro.</li> </ul>                                                                                                                                                                                                                                  |
| Nanoparticles of ZnO and $TiO_2$<br>(ZnO in composites and $TiO_2$ in adhesives)                       | <p><i>Antimicrobial</i></p> <ul style="list-style-type: none"> <li>• Incorporation of ZnO nanoparticles in composites significantly inhibit the growth of <i>S. mutans</i></li> <li>• <math>TiO_2</math> has well-known pathogenicidal effects. <math>TiO_2</math> nanoparticles in dental adhesive materials yielded a strong antibacterial effect</li> </ul>                                                                                                                                                                       |

shown that NAg imparts a strong antibacterial activity to dental resins, greatly reducing biofilm growth and lactic acid production, without negatively affecting the other physical and mechanical properties of the resins. NAg could be used alone in the resin for antibacterial activity, or together with other bioactive agents to obtain desirable properties.



**Fig. 9.2** Schematic representation of a bacterial cell depicting its various components targeted by nanoparticles of silver, zinc oxide, and quaternary ammonium polyethylenimine.

Lei Cheng et al. carried out a study to develop novel nanocomposites containing nanoparticles of both calcium phosphate (NACP) and silver (NAg) to achieve caries-inhibiting and remineralizing capabilities. They found that the dual benefits of antibacterial and remineralization capabilities in composites could be achieved if NACP and NAg were combined without adversely affecting the load-bearing properties of the composite to resist chewing forces in vivo [17].

#### 9.4.1.2 Zinc oxide nanoparticles (ZnO-NP)

Similar to silver, zinc oxide (ZnO) has demonstrated antibacterial effects against several types of bacteria, including *S. mutans*. The main mechanism by which nanoparticles of zinc (NZn) exert antimicrobial activity is generation of reactive oxygen species, such as superoxide anion ( $O_2^-$ ), hydrogen peroxide ( $H_2O_2$ ), and hydroxide ( $OH^-$ ). These species cause destruction of cellular components such as lipids, DNA, and proteins of bacterial cells inhibiting its growth [18]. Another potential antimicrobial mechanism of ZnO-NP occurs via the release of zinc ions in a medium containing ZnO-NPs and bacteria. The released  $Zn^{2+}$  actively inhibits the active transport and metabolism of sugar, as well as disrupts enzyme systems of dental biofilms by displacing magnesium ions essential for enzymatic activity of the plaque [19] (Fig. 9.2). Dental composites containing 10% NZn moderately reduce bacterial counts and biofilm growth. However, the antibacterial efficacy was lower when compared with that found for NAg-containing composites [20].

### 9.4.1.3 Quaternary ammonium polyethylenimine (QA-PEI) nanoparticles

The mechanism of action of antibacterial quaternary ammonium compounds is believed to be a sequence of events beginning with cationic binding and electrostatic interaction between the nanoparticles of QA-PEI, and the microorganism's cell wall components, resulting in strong adsorption that later disrupts membrane function and leads to leakage of constituents such as  $K^+$  ions, DNA, and RNA, and culminates in cell death [21] (Fig. 9.2). Polymers containing quaternary ammonium salts (QAS) have been incorporated into dental composites and dental adhesives. QAS have the advantage that the antibacterial agent is copolymerized with the resin by forming a covalent bond with the polymer network, and therefore is immobilized in the composite and not released or lost over time. Adhesive systems containing QAS presented similar antibiofilm properties after 6 months of water aging [22]. Quaternary ammonium polyethylenimine (QAS-PEI) nanoparticles were incorporated in composite resins to improve antibacterial activity and reduce adverse effects on mechanical properties further [21]. It has been shown that the incorporation of 1% QAS-PEI nanoparticles in dental composite resin exhibited an immediate and strong antibacterial effect against *S. mutans* sustained over 1 month without leaching out and with no alteration of the original mechanical properties of the composite [23].

### 9.4.1.4 Titanium oxide ( $TiO_2$ )

$TiO_2$  has well-known pathogenicidal effects. The use of  $TiO_2$  nanoparticles in dental adhesive materials yielded a strong antibacterial effect [24].

## 9.4.2 Remineralizing nanocomposites (containing nanoparticles of calcium phosphate, calcium fluoride, nanohydroxyapatite, and nanofluorohydroxyapatite)

### 9.4.2.1 Calcium phosphate nanoparticles

The main problem limiting the longevity of composite restorations are secondary caries. Composites containing nanoparticles of amorphous calcium phosphate (NACP) are considered “smart,” and have been shown to release Ca and P ions and remineralize tooth lesions at cariogenic low pH levels [25]. Composites containing nanoparticles of amorphous calcium and phosphate ions release calcium, and phosphate ions, similar to traditional composites, but with a two-fold increase in flexural strength and elastic modulus for load-bearing restorations. Furthermore, composites containing NACP effectively neutralized a lactic acid challenge, while commercial control restoratives failed to neutralize the acid. NACP nanocomposites are promising for high-caries-risk patients; for those with dry mouth, such as senior patients; and in cavities where complete removal of caries tissues is contra-indicated [26].

### 9.4.2.2 Calcium fluoride nanoparticles

Fluoride aids in remineralization and inhibits acid production by cariogenic bacteria. Unfortunately, current dental materials with high fluoride release generally have

poor mechanical properties, or release only a small amount of fluoride with low fluoride-recharge capability. Dental composites with calcium fluoride (CaF<sub>2</sub>) nanoparticles exhibits high fluoride release, but still maintain strength and wear resistance [27]. Cumulative fluoride release increases with nano-CaF<sub>2</sub> content, and composites containing 20%–30% CaF<sub>2</sub> nanoparticles match. Dental composites with calcium fluoride (CaF<sub>2</sub>) nanoparticles exhibit high fluoride release, maintaining strength and wear resistance. Previous studies showed higher fluoride release from the CaF<sub>2</sub> nanoparticles at cariogenic low pH (<5.5). Directing these ions when they would be most needed to inhibit caries was achieved without compromising long-term mechanical properties [28].

#### 9.4.2.3 Nanohydroxyapatite (NHA)

Synthetic hydroxyapatite is a biologically compatible material, and is a logical compound substitute for the natural mineral constituent of dentin. Its applicability in biomaterials by addition of HA powders to restorative dental materials for remineralization effects and improvement of mechanical properties has been investigated due to its excellent biocompatibility and bioactivity. For remineralization of teeth, hydroxyapatite (HA; Ca<sub>10</sub>(PO<sub>4</sub>)<sub>6</sub>(OH)<sub>2</sub>) nanoparticles were investigated. A 10% suspension containing nano-HA particles (10–20 nm diameter; 60–80 nm length) promoted remineralization of the superficial layer of the initial caries lesions to a depth of 20–40 μm; however, little remineralization could be obtained in the body of the lesion [29].

## 9.5 Conclusion

The application of nanotechnology is a promising field for inhibiting biofilm formation, regulating the demineralization and remineralization of teeth, and for prevention and treatment of tooth decay. Nanoparticles of silver and quaternary ammonium compound have received particular attention as a result of their strong antimicrobial activity. Calcium phosphate and calcium fluoride nanoparticles have the capability of enhancing remineralization. Incorporation of nanoparticles into dental composites and adhesives could have double benefits: antibacterial capability, and remineralization of tooth lesions. In view of recurrent caries at the tooth-restoration margins as the main factor for restoration failures, the novel nanocomposite and nanostructured adhesives with an effective caries inhibiting capability are promising for a wide range of dental applications. Novel agents such as NAg, NACP, QAMs, and others are promising for use in various dental composites, adhesives, cements, and sealants to inhibit dental caries.

## References

- [1] A. Mnyusiwalla, A.S. Daar, P.A. Singer, “Mind the gap”: science and ethics in nanotechnology, *Nanotechnology* 14 (2003) R9–R13.
- [2] M.C. Roco, Nanotechnology: convergence with modern biology and medicine, *Curr. Opin. Biotechnol.* 14 (2003) 337–346.

- [3] M. Ferrari, Cancer nanotechnology: opportunities and challenges. *Nat. Rev. Cancer* 5 (2005) 161–171, <https://doi.org/10.1038/nrc1566>.
- [4] O. Fejerskov, E. Kidd (Eds.), *Dental Caries the Disease and Its Clinical Management*, Blackwell Munksgaard, Oxford, 2008, pp. 209–231.
- [5] D.M. Deng, J.M. Ten Cate, Demineralization of dentin by *Streptococcus mutans* biofilms grown in the constant depth film fermentor, *Caries Res.* 38 (1) (2004) 54–61.
- [6] J.A. Cury, L.M. Tenuta, Enamel remineralization: controlling the caries disease or treating early caries lesions? *Braz. Oral Res.* 23 (2009) 23–30.
- [7] M. Fontana, et al., Defining dental caries for 2010 and beyond, *Dent. Clin. N. Am.* 54 (2010) 423–440.
- [8] J.L. Ferracane, Resin composite-state of the art, *Dent. Mater.* 27 (2011) 29–38.
- [9] S. Kasraei, L. Sami, S. Hendi, M.Y. Alikhani, L. Rezaei-Soufi, Z. Khamverdi, Antibacterial properties of composite resins incorporating silver and zinc oxide nanoparticles on *Streptococcus mutans* and *Lactobacillus*, *Restor. Dent. Endod.* 39 (2) (2014) 109–114.
- [10] C. Chen, M.D. Weir, L. Cheng, et al., Antibacterial activity and ion release of bonding agent containing amorphous calcium phosphate nanoparticles, *Dent. Mater.* 30 (8) (2014) 891–901.
- [11] D.R. Monteiro, L.F. Gorup, A.S. Takamiya, A.C. Ruvollo-Filho, E.R. De Camargo, D.B. Barbosa, The growing importance of materials that prevent microbial adhesion: antimicrobial effect of medical devices containing silver, *Int. J. Antimicrob. Agents* 34 (2) (2009) 103–110.
- [12] M. Rai, A. Yadav, A. Gade, Silver nanoparticles as a new generation of antimicrobials, *Biotechnol. Adv.* 27 (1) (2009) 76–83.
- [13] J.S. Kim, E. Kuk, K. Yu, J.H. Kim, S.J. Park, H.J. Lee, S.H. Kim, Y.K. Park, Y.H. Park, C.-Y. Hwang, Y.K. Kim, Y.S. Lee, D.H. Jeong, M.H. Cho, Antimicrobial effects of silver nanoparticles, *Nanomedicine* 3 (2007) 95–101.
- [14] K. Yamamoto, S. Ohashi, M. Aono, T. Kokubo, I. Yamada, J. Yamauchi, Antibacterial activity of silver ions implanted in SiO<sub>2</sub> filler on oral streptococci, *Dent. Mater.* 12 (4) (1996) 227–229.
- [15] K. Yoshida, M. Tanagawa, M. Atsuta, Characterization and inhibitory effect of antibacterial dental resin composites incorporating silver-supported materials, *J. Biomed. Mater. Res.* 47 (4) (1999) 516–522.
- [16] Y.J. Cheng, D.N. Zeiger, J.A. Howarter, et al., In situ formation of silver nanoparticles in photocrosslinking polymers, *J. Biomed. Mater. Res. B Appl. Biomater.* 97 (1) (2011) 124–131.
- [17] L. Cheng, M.D. Weir, H.H. Xu, et al., Effect of amorphous calcium phosphate and silver nanocomposites on dental plaque microcosm biofilms, *J. Biomed. Mater. Res. B Appl. Biomater.* 100 (5) (2012) 1378–1386.
- [18] M. Premanathan, K. Karthikeyan, K. Jeyasubramanian, G. Manivannan, Selective toxicity of ZnO nanoparticles toward Gram-positive bacteria and cancer cells by apoptosis through lipid peroxidation, *Nanomedicine* 7 (2) (2011) 184–192.
- [19] Y. Xie, et al., Antibacterial activity and mechanism of action of zinc oxide nanoparticles against *Campylobacter jejuni*, *Appl. Environ. Microbiol.* 77 (2011) 2325–2331.
- [20] B.A. Sevinc, L. Hanley, Antibacterial activity of dental composites containing zinc oxide nanoparticles, *J. Biomed. Mater. Res. B Appl. Biomater.* 94 (2010) 22.
- [21] N. Beyth, I. Yudovin-Farber, R. Bahir, A.J. Domb, E.I. Weiss, Antibacterial activity of dental composites containing quaternary ammonium polyethylenimine nanoparticles against *Streptococcus mutans*, *Biomaterials* 27 (21) (2006) 3995–4002.

- [22] K. Zhang, et al., Effect of water-ageing on dentine bond strength and anti-biofilm activity of bonding agent containing new monomer dimethylaminododecyl methacrylate, *J. Dent.* 41 (2013) 504–513.
- [23] N. Beyth, et al., Long-term antibacterial surface properties of composite resin incorporating polyethyleneimine nanoparticles, *Quintessence Int.* 41 (2010) 827–835.
- [24] K. Welch, Y. Cai, H. Engqvist, M. Strømme, Dental adhesives with bioactive and on-demand bactericidal properties, *Dent. Mater.* 26 (5) (2010) 491–499.
- [25] S.E. Langhorst, J.N. O'Donnell, D. Skrtic, *In vitro* remineralization of enamel by polymeric amorphous calcium phosphate composite: quantitative microradiographic study, *Dent. Mater.* 25 (2009) 884–891.
- [26] R.Z. LeGeros, in: H.M. Myers (Ed.), *Calcium Phosphates in Oral Biology and Medicine*, S. Karger, Basel, Switzerland, 1991 (Chapters 3–4).
- [27] M.J. Tyas, K.J. Anusavice, J.E. Frencken, G.J. Mount, Minimal intervention dentistry—a review FDI commission project 1-97, *Int. Dent. J.* 50 (2000) 1–12.
- [28] L. Sun, L.C. Chow, Preparation and properties of nano-sized calcium fluoride for dental applications, *Dent. Mater.* 24 (2008) 111–116.
- [29] N. Roveri, B. Palazzo, M. Iafisco, The role of biomimetism in developing nanostructured inorganic matrices for drug delivery, *Expert Opin. Drug Deliv.* 5 (8) (2008) 861–877.