BioCoat™

Part 1. Technology

premier® Inspired solutions for daily dentistry™

Introduction

Dental caries and periodontal disease are multifactorial, polymicrobial diseases with a high worldwide prevalence. An estimated 23% of children 2 to 5 years-of-age and 56% of children 6 to 8 years-of-age in the United States have dental caries in their primary dentition.1 In adults between 20 and 64 years-of-age, an estimated 91% have experienced dental caries in their permanent dentition.[2] In addition, recurrent caries is a frequent reason for restoration replacement.[3,4] Caries risk factors include, but are not limited to poor oral hygiene, a diet rich in fermentable carbohydrates, and a lack of exposure to protective factors.[5] With respect to periodontal disease, in the United States it is estimated that between 50% and 94% of adults have gingivitis and 47% have chronic periodontitis.[6-8] Globally, up to 75% of the population is estimated to experience gingivitis.[9] Caries experience for children from age 6 through adolescence is estimated at a worldwide average of 70%.[9]

The presence of cariogenic bacteria is a prerequisite for dental caries.[5] These bacteria metabolize fermentable carbohydrates to produce acid that decreases the pH in dental plaque. If conditions are unfavorable, acid diffuses into the tooth and demineralization of tooth structure occurs.[5,10] This results in the loss of calcium and phosphate ions into solution from the hydroxyapatite crystals (HAP).10 In dentin, demineralization is followed by enzymatic degradation of the exposed dentin fibrils,[11] resulting in a faster rate of caries progression than in enamel.

Regular and thorough mechanical removal of dental plaque reduces the presence of dental biofilm, and chemotherapeutic antimicrobial agents kill and/or inhibit cariogenic bacteria. When conditions are favorable for oral health, demineralization is inhibited and, if it occurs, is rapidly followed by remineralization. Fluoride has been widely used to help control dental caries, to inhibit demineralization and promote remineralization of HAP, replacing lost ions to form fluorapatite which is more acid resistant than HAP.[12-16] In addition, calcium is essential for remineralization.[17]

Increasing exposure to protective factors such as calcium, phosphate and fluoride ions helps to create conditions favorable for oral health.[12-18] Similarly, antimicrobials help to reduce levels of recognized cariogenic and periodontal bacteria, as well as other bacteria that may play a role in these diseases.[19-21]

The current paper reports on research on SmartCap Technology, and assesses the potential of this promising technology in for applications in dentistry.

SmartCap Technology - Microcapsules

SmartCap Technology is used to create novel microcapsules with a polyurethane-based shell which functions as a semi-permeable membrane. This technology enables the incorporation of aqueous solutions into the microcapsules that could contain, for instance, anti-caries or antimicrobial agents. The microcapsules can further be embedded into dental materials/products.

The microcapsules are created by using aqueous and oil phases that are mixed to form an emulsion.[22,23] After adding energy, reverse emulsification occurs and microcapsule formation begins (Figure 1) when a polymerizable agent that is both hydrophilic and lipophilic is added. The resulting microcapsules are between 1 and 2 micrometers in size.[22] (Figure 2)

Figure 1. Process for creation of microcapsules[22]

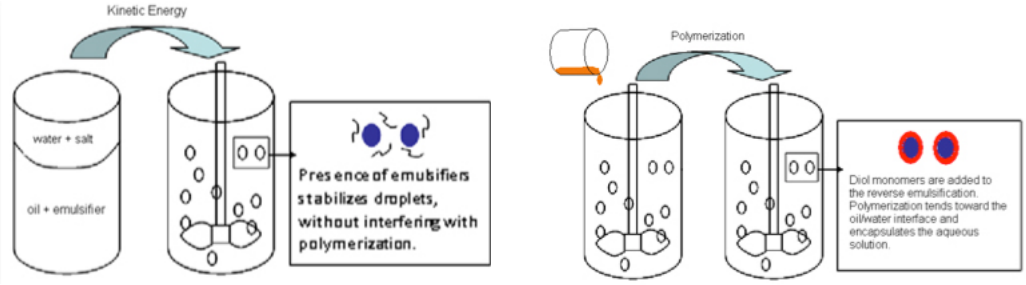
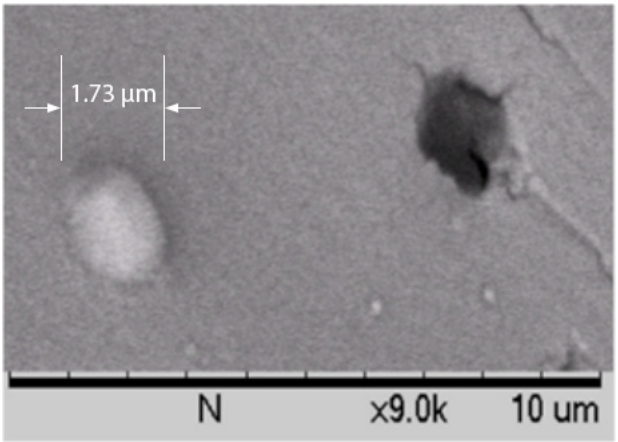


Figure 2. SEM of microcapsule[22]



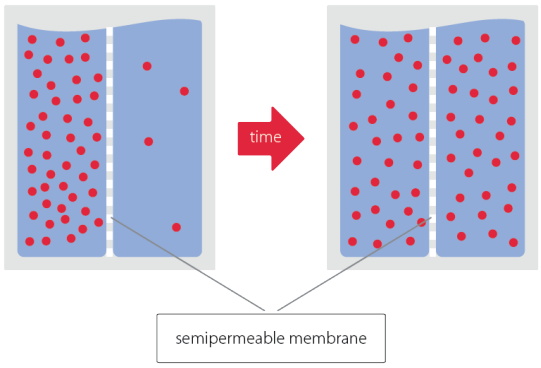
The microcapsule's shell offers two-way permeability and thereby permits the aqueous solution containing the desired agent, e.g., calcium, phosphate and fluoride solutions, to enter the microcapsules. Subsequently, the two-way permeability permits the release of bioavailable ions from the microcapsules into the surrounding environment.[22,24]

In addition, the microcapsule's shell enables influx of the same ions into the microcapsules to replenish the amount present within them.

Mechanisms: Concentration gradients and diffusion of ions

When a concentration gradient exists, for instance across a semi-permeable membrane, diffusion from the higher concentration to the lower concentration of the ions/molecules through the membrane occurs. This results in maintaining the equilibrium. (Figure 3)

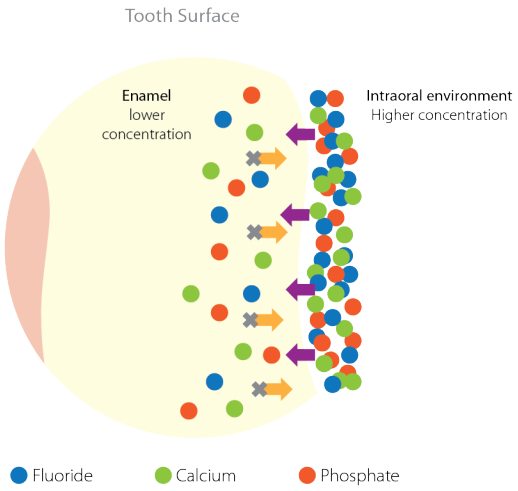
Figure 3. Concentration gradients and ion diffusion



One example is related to demineralization and remineralization. In dentistry, an example of this phenomenon involves fluoride. When topical fluoride is used, this results in the formation of calcium fluoride-like globules at the tooth surface (firmly-bound) and in plaque (loosely-bound).[25-29] These globules release calcium, fluoride and phosphate ions when the local pH declines. This results in a concentration gradient, with a higher concentration of fluoride, calcium and phosphate ions at the tooth surface compared to within the tooth structure. (Figure 4) Demineralization is thereby inhibited and remineralization promoted, with diffusion of the ions into the tooth structure.

The same phenomenon is utilized in SmartCap Technology. By creating a microcapsule that contains the desired agent in a concentrated aqueous solution encapsulated in a semi-permeable membrane, bioavailable ions can move freely across the membrane (i.e., diffuse through it) to the adjacent areas. The concentration gradient allows for movement from the higher to the lower concentration areas. Surprisingly, only small amounts of released ions are required to exert an effect. A notable example is the caries reductions achieved with water fluoridation at miniscule levels of 0.7 to 1 part per million.[30]

Figure 4. Concentration gradients in anti-caries activity



Water sorption of resin composites

It needs to be noted that all dental resin composites are porous to some degree, including those that release fluoride or other substances.[31] The fact that the microcapsules freely permit the movement of water into and through them results in a distinct advantage such that the structural volume of the microcapsules remains essentially unchanged over time. This is because the microcapsules are composed of monomers similar to the substrate which adds additional structural integrity. Furthermore, the porosity of the resin material (substrate) allows ions to move through in both directions: from the microcapsules to increase the concentration at the tooth-material interface, and into the microcapsules to replenish ions from external sources (such as rinses or toothpastes). However, since only a small amount is released over time, even without recharge there is long-term availability of the ions from within the microcapsules. In addition, the sustained release can be designed and controlled.

For all research conducted to evaluate the effects of these factors, the release of phosphate ions was measured using the classic molybdenum blue test, whereby a Tecan Infinite M200 spectrophotometer was utilized to measure the absorbance values of the molybdenum complex at 882 nm.[32] The release of calcium and fluoride were measured using ion specific electrodes.

Controlling ion release from SmartCap Technology microcapsules

The rate of release of bioavailable ions can be controlled by varying the chemical structure of the microcapsule shell. Other variables offering the ability to control the rate of ion release include the concentration (molarity) of the aqueous solution within the microcapsules, characteristics of the substrate in which the microcapsules are embedded, temperature, and the counterion used for the aqueous solution (e.g., whether calcium is combined with nitrate, chloride or acetate as the counterion to form a calcium-based compound).[24,33,34] (Table 1)

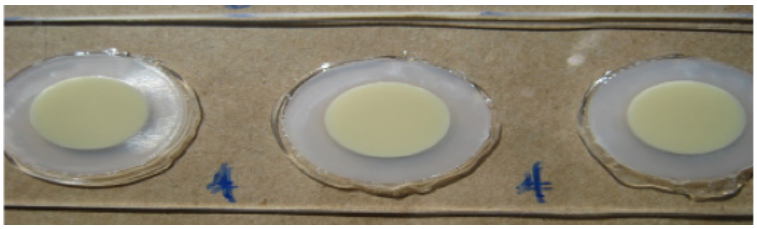
Table 1. Variables influencing the rate of ion release from SmartCap microcapsules[33]

Structure of the microcapsule's shell
Concentration of the aqueous solution within microcapsules
Counterion used
Characteristics of the substrate for the microcapsules
Temperature

Chemical structure of the microcapsule shell

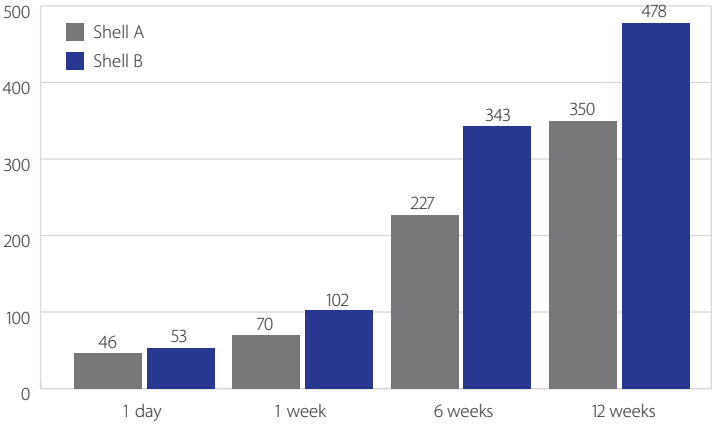
The structure of the microcapsule shell influences the ion release profile, as demonstrated in a study with resin- and rosin-based varnishes.[35] Two types of polyurethane-based shells were used, and a 2.4 molar aqueous solution of potassium phosphate dibasic was used as the charging solution for the embedded microcapsules in the varnishes. To ensure that the same surface areas of set varnish were exposed, the varnish formulations were placed in o-rings, mounted on glass slides and set to dry. (Figure 5). After setting, the slides were placed in nanopure water and samples taken at predetermined intervals to assess phosphate ion release from the microcapsules.

Figure 5. Varnish formulation in o-rings and plated on slides[35]



The results showed that the composition of the microcapsule shell and the substrate both influenced ion release at each time point. Figure 6 shows the results for the rosin-based formulation, confirming the effect of the microcapsule shell composition.[35]

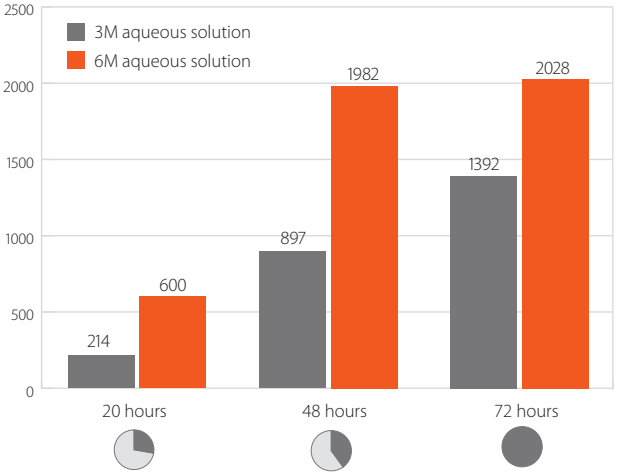
Figure 6. Phosphate ion release (ppm) for rosin varnish with microcapsules[35]



Concentration of the aqueous solution

Increasing the concentration (molarity) of the aqueous solution within SmartCap Technology microcapsules significantly increases the rate of ion release.[36] (Figure 7)

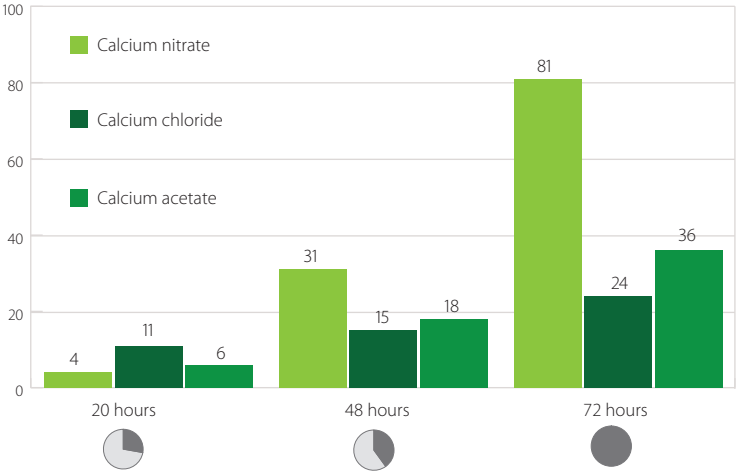
Figure 7. Rate of phosphate ion release (ppm) with differing aqueous solution concentrations[36]



Counterion effect

The use of aqueous solutions containing calcium nitrate, calcium chloride or calcium acetate and the resulting calcium ion release from microcapsules was investigated. The counterion used (nitrate or chloride or acetate) was found to significantly influence the rate of release of ions.[36] (Figure 8)

Figure 8. Ion release profile and the influence of the aqueous solution's counterion[36]

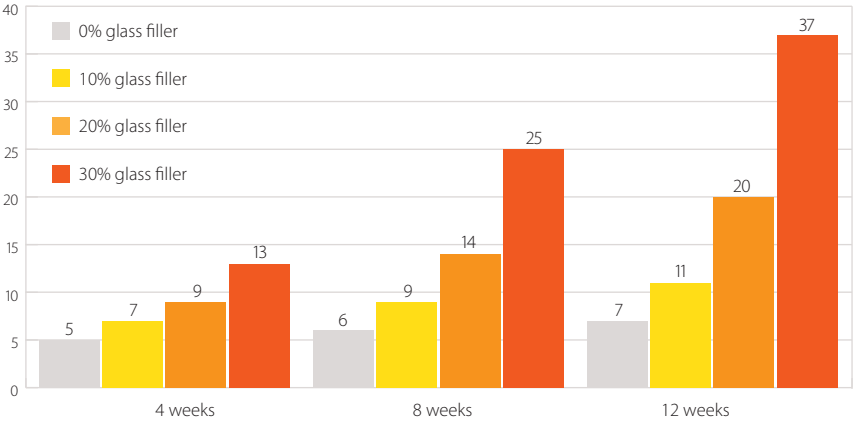


Dental materials and SmartCap Technology – resin-based formulations

Glass filler content: The phosphate ion release profile for resin-based glaze formulations with 15% w/w microcapsules containing 4 molar potassium phosphate dibasic was investigated over a period of 12 weeks.[37] Phosphate ion release was found to vary with the proportion of glass filler in the formulation. As with the varnish study described earlier, the glaze formulation was placed in o-rings, then transferred to a slide and set, before being placed in nanopure water. The liquid was then sampled at predetermined intervals to measure phosphate

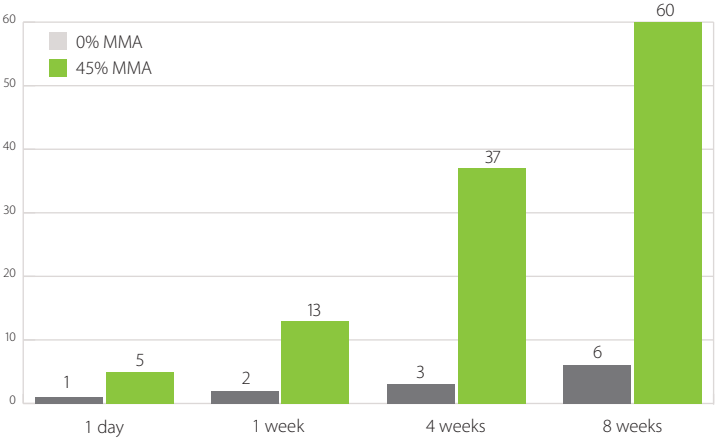
ion release. While the ion release was identical on day 1 and similar at 1 week for all tested filler content levels, progressively more phosphate ions were released at higher filler content levels over time. By week 12, 37 ppm phosphate/gram of glaze formulation was released from the 30% glass filler formulation compared with 7 ppm/gram, 11 ppm/gram and 20 ppm/gram for 0%, 10% and 20% glass filler, respectively.[37] (Figure 9)

Figure 9. Phosphate ion release from resin-based glaze formulations by filler content[37]



Methyl methacrylate concentration: Methyl methacrylate (MMA) content in a glass formulation was found to influence phosphate and calcium ion release from 15% w/w SmartCap ion-permeable microcapsules containing 4 molar potassium phosphate dibasic or 4 molar calcium nitrate solutions.38 During this 8-week study, calcium and phosphate ion release was significantly higher at all time periods for glaze formulations containing 45% MMA. Figure 10 shows calcium ion release at 0% and 45% MMA content.[38]

Figure 10. Calcium ion release (ppm) at 0% and 45% MMA[38]



Dental materials and SmartCap Technology – varnish formulations

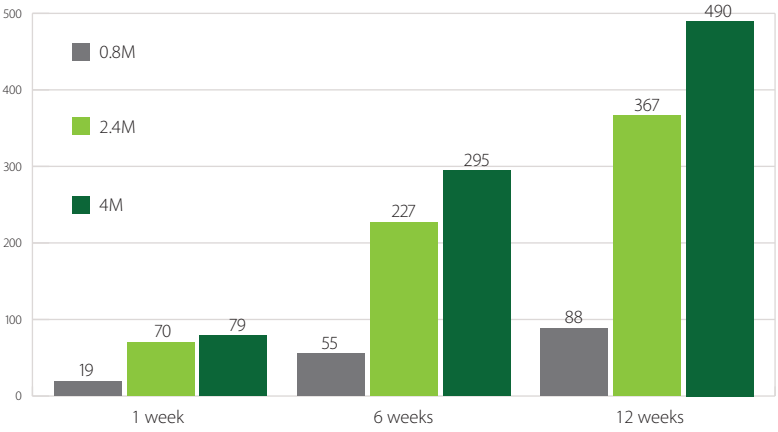
In assessing the effect of microcapsules incorporated into resin or rosin varnishes, it was found that 15% w/w of microcapsules with 0.8 molar potassium phosphate dibasic, calcium nitrate or sodium fluoride all resulted

in increased release over time of the respective bioavailable ion.[39] (Table 2) Additionally, changing the molarity (concentration) of the aqueous solution within the microcapsules showed the ability to influence the rate and profile of the ion release from the varnishes.[39,40] (Figure 11)

Table 2. Ion release from 0.8 molar aqueous solutions in a varnish containing 15% wt. microcapsules.[39]

Continuous Phase	Ion Release Measured	Initial Conc. in Microcapsules (M)	Weight % of microcapsules	1 day (ppm)	1 Week (ppm)	6 weeks (ppm)	12 weeks (ppm)
Resin	Phosphate	0.8	15	3	4	12	20
Resin	Calcium	0.8	15	1	3	10	15
Resin	Fluoride	0.8	15	0.4	0.6	1	1
Rosin	Phosphate	0.8	15	5	31	70	75
Rosin	Calcium	0.8	15	2	7	24	28
Rosin	Fluoride	0.8	15	0.5	5	19	22

Figure 11. Phosphate ion release profile (ppm) from varnish formulation based on molarity (concentration) of the aqueous solution in the microcapsules[40]



In other research, microcapsules incorporating monomer/accelerator or initiator have been shown to induce self-healing of fractured resin-based composite.[41] The control material consisted of 45% resin matrix in a 1:1:1 ratio (by weight) of bis-GMA/UDMA/TEGDMA and 55% silanated glass, to which the photoinitiators were then added for light curing. For the experimental composite material, microcapsules containing TEGDMA with accelerator and microcapsules containing benzoyl peroxide (BPO) as a catalyst were incorporated into the resin phase. The microcapsules replaced the same amount in the resin matrix, such that the 45% resin phase contained the microcapsules and 55% silanated glass was maintained.[41] The experimental material was loaded to fracture, self-healing was allowed to occur and the material was subsequently again loaded to fracture. In comparing the fracture toughness during the first and second loading, a 49% recovery rate was observed for the expermental material, demonstrating its self-healing capabilities. Further research is being conducted to enhance composite self-healing capabilites.[41]

Incorporation of SmartCap Technology into toothpaste

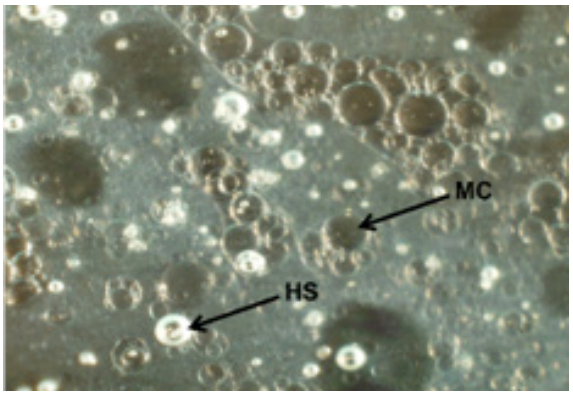
Promising results have been observed for a commercially available fluoride toothpaste formulation, with the additional incorporation of 5% w/w microcapsules containing an aqueous solution of 3 molar calcium nitrate or 5 molar potassium phosphate dibasic.[42] For each formulation, 1 gram of toothpaste was placed in 10 ml of nanopure water and brushed for 1 minute to obtain a slurry that was used for ion content analysis. The results showed that bioavailable calcium or phosphate ion release was significantly higher in the respective microcapsule-enriched toothpaste formulation. In addition, the results demonstrated the ability to influence the release of all 3 ions in an interrelated manner based on the aqueous solution in the microcapsules.[42] (Table 3).

Table 3. Ion release (ppm) with and without microcapsules[42]

Ion Release	No Microcapsules (ppm)	5 wt% of 3M Ca(NO3)2 Microcapsules (ppm)	5 wt% of 5M K2HPO4 Microcapsules (ppm)
Fluoride	66	15	65
Calcium	0.7	210	0.5
Phosphate	1.5	0.6	1020

Secondly, microcapsules containing 6 molar calcium nitrate or 4 molar potassium phosphate dibasic were incorporated into a fluoride toothpaste at 5% w/w.[42] Figure 12 shows a stereomicroscopic image of the toothpaste with microcapsules containing an aqueous calcium salt solution. A comparison was made of the ion release from slurries obtained after 2 minutes of brushing with 1g toothpaste in 12 ml of nanopure water (the brushing time mimicking recommendations for regular oral hygiene) and 2 minutes of soaking. Brushing typically ruptured the microcapsules after 3 brush strokes.[42] (Figures 13a, b)

Figure 12. Stereomicroscopic image of toothpaste containing microcapsules that contain an aqueous calcium salt solution.[42]



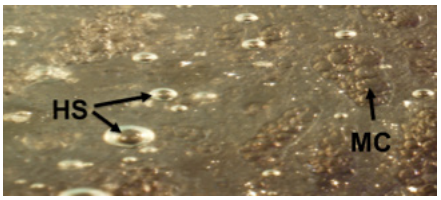


Figure 13a. Toothpaste showing

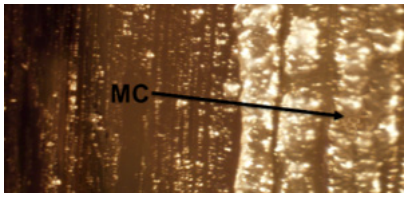


Figure 13b. Toothpaste showing ruptured microcapsules (no brushing)
microcapsules after brushing

For comparison, a control using non-brushed samples soaked in nanopure water for 4 minutes was also evaluated for ion release. The results unequivocally demonstrated the positive effect of brushing on ion release. Tables 4-6 show the effect of brushing on the fluoride, calcium and phosphate ion release from the tested toothpaste formulations.[42]

Table 4. Fluoride ion release (ppm) for brushed and non-brushed samples[42]

Formulation	Non-Brushed Samples (ppm fluoride ion released)	Brushed Samples (ppm fluoride ion released)
Control, No Microcapsules	2.8	63
5 wt% Calcium Microcapsules	1.1	50
5 wt% Phosphate Microcapsules	0.8	70
5 wt% Calcium Microcapsules and 5 wt% Phosphate Microcapsules	0.5	38

Table 5. Phosphate ion release (ppm) for brushed and non-brushed samples[45]

Formulation	Non-Brushed Samples (ppm phosphate ion released)	Brushed Samples (ppm phosphate ion released)
Control, No Microcapsules	2.2	7.9
5 wt% Phosphate Microcapsules	38	1350
5 wt% Calcium Microcapsules and 5 wt% Phosphate Microcapsules	38	935

Table 6. Calcium ion release (ppm) for brushed and non-brushed samples[45]

Formulation	Non-Brushed Samples (ppm fluoride ion released)	Brushed Samples (ppm fluoride ion released)
Control, No Microcapsules	0.0	0.1
5 wt% Calcium Microcapsules	3.8	370
5 wt% Calcium Microcapsules and 5 wt% Phosphate Microcapsules	2.6	100

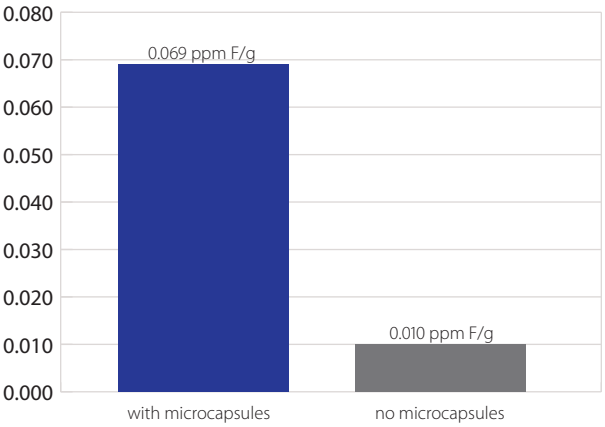
Fluoride adsorption/absorption and recharge

The ability of a material to adsorb fluoride (onto the material's surface)/absorb fluoride (into the material), and to later release this, is advantageous for protection against dental caries. Fluoride released following its adsorption/absorption from a fluoride toothpaste slurry (50% w/w toothpaste and 50% w/w water) was measured for a film of RBS material with no microcapsules and for one with 7% w/w microcapsules containing only nanopure water.[43] The film surface was brushed for 2 minutes with 0.4 ml of the slurry, and this was repeated 40 times, each time with fresh toothpaste slurry. (Figure 14) The samples were subsequently rinsed free of toothpaste slurry, dried and placed in nanopure water. Samples of the fluid were taken over 2 weeks to measure its fluoride ion concentration to evaluate fluoride ion release from the samples. Significantly more fluoride was released from the sealant containing microcapsules, believed to be attributable to the ability of the microcapsules (which previously only contained nanopure water) to incorporate fluoride.[43] (Figure 14)

Figure 14. Brushing toothpaste slurry on the film surfaces[43]

Fluoride absorption and release in an orthodontic cement formulation has been investigated using the same method.[44] An orthodontic resin-based composite cement was formulated with microcapsules containing nanopure water, and another without microcapsules as the control. The samples of orthodontic cement were then brushed for 2 minutes with 0.4 ml of fluoride toothpaste slurry (50% w/w toothpaste and 50% w/w water). This was repeated 40 times, with the samples being rinsed with nanopure water and wiped between brushings. Next, the samples were rinsed free of toothpaste slurry, dried and placed in separate containers with nanopure water. Fluid samples were taken for each one periodically over 2 weeks, to measure their fluoride ion concentration and evaluate fluoride ion release from the samples. At 2 weeks, the orthodontic cement containing microcapsules released 0.069 ppm fluoride/gram of cement compared with 0.010 ppm for the formulation containing no microcapsules.[44] (Figure 15)

Figure 15. Fluoride release at 2 weeks in orthodontic cement with and without semi-permeable microcapsules[44]



Recharge efficacy of microcapsules

Effective recharge of aqueous solutions has also been demonstrated, together with the ability to adjust recharge by varying the concentration of the recharging solutions and length of exposure to it. In one study, four sets of microcapsules containing nanopure water that were soaked in 0.8 molar potassium phosphate dibasic for 1 hour, 3 hours, 6 hours, and 12 hours to "charge" the microcapsules with ions.[33] After rinsing the microcapsules and placing them in nanopure water, samples of the liquid were taken to measure phosphate ion release. Increasing the length of exposure increased ion release.[45] Differing concentrations of the charging solution also resulted in significant differences between the samples.[45] Measurements for this test were taken at 1 hour, 4 hours, 12 hours and 24 hours. The study demonstrated that exposure to a solution resulted in differing diffusion of ions into the microcapsules. Further, the relationship was not linear, with peak exposure at 0.8 molar.[45] (Table 7)

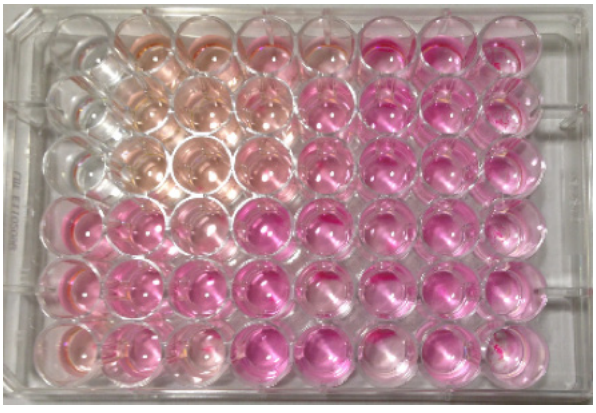
Table 7. Phosphate ion charging by solution concentration and length of exposure[45]

Salt in the recharging solution	Concentration of charging solution	1 hour (ppm)	4 hours (ppm)	12 hours (ppm)	24 hours (ppm)
Potassium phosphate dibasic	0.4	3	10	17	22
Potassium phosphate dibasic	0.8	15	31	86	125
Potassium phosphate dibasic	1.6	7	14	35	59
Potassium phosphate dibasic	2.4	2	3	4	4
Calcium Nitrate	0.8	24	59	145	167

Research on SmartCap Technology and antimicrobial agents

In other research, microcapsules were created incorporating an aqueous solution of benzalkonium chloride, a proven antimicrobial agent.46 The microcapsules were embedded in a sealant formulation. Benzalkonium release was confirmed and measured using an Eosine Y dye-based uv/vis detection method to detect benzalkonium cations.[46] (Figure 16)

Figure 16. Eosine Y dye-based detection method for release of benzalkonium cations[46]



In a second study on aqueous solutions of antimicrobial agents, benzalkonium chloride and cetylpyridinium chloride were selected as the antimicrobial agents.[47] Testing was conducted using different antimicrobial concentrations and different microcapsule shells. Detection of antimicrobial release again used the Eosine Y dye-based uv/vis detection method. The release of benzalkonium (ppm/g microcapsules) generally increased as the concentration of the antimicrobial agent increased. However, the release profile showed a dip at a concentration of 7.5% w/w before increasing further with a concentration of 10% w/w. Overall, while increases were observed over time for each concentration, these were not linear. (Figure 17) In addition, the release of benzalkonium was significantly greater than for cetylpyridinium and their release profile differed.[47] (Figure 18)

Figure 17. Normalized release at varying concentrations of benzalkonium chloride[47]

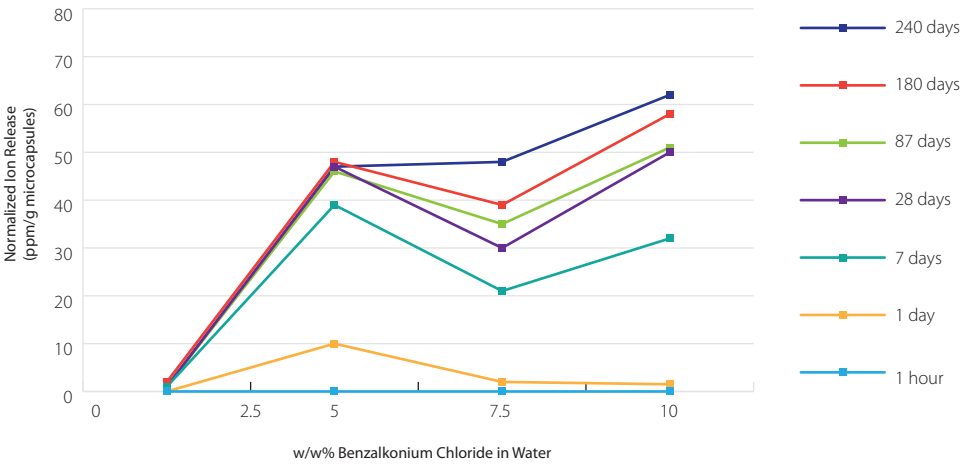
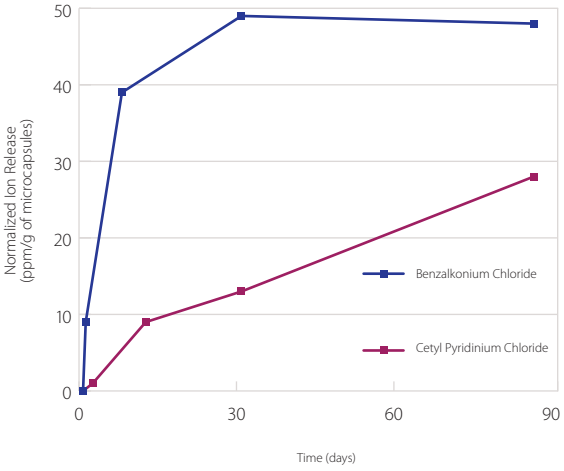


Figure 18. Release profiles for benzalkonium and cetylpyridinium contained in microcapsules[47]



Discussion

Topical fluorides are a mainstay of caries control, and their use results in the presence of calcium fluoride-like globules at the tooth surface and in plaque. The calcium fluoride-like globules act as a reservoir, releasing bioavailable calcium, fluoride and phosphate ions.[25,28,29] This is believed to occur when the phosphate coating is disrupted in response to a lowering of the local pH during acid attacks. As a result, the concentration gradient of fluoride, calcium and phosphate ions is higher at the tooth surface than within the tooth structure. This leads to

inhibition of demineralization and promotes remineralization by diffusion of the fluoride into the tooth structure, together with the other ions.[27,29,30] In addition, free fluoride ions are present intraorally and fluoride is also "bonded" to bacteria or their fragments by calcium-fluoride bonds.[16,25] It is important to note that calcium is essential for remineralization.[17]

Products containing bioactive materials, as well as calcium and phosphate technologies, are currently available and evidence suggests that these are protective and help to remineralize tooth structure by delivering fluoride, calcium and phosphate ions.[17,18,48] This increases the concentration of these ions at the tooth surface. Together with fluoride added in the product or already present intraorally, this provides a higher concentration at the tooth surface than within the hard tissue structure. Studies show these technologies now deliver or create HAP components with use.

SmartCap Technology is a unique method of storing and delivering the active ingredients that can contribute to the control of dental caries. Given that the microcapsules can be exposed to aqueous solutions containing fluoride, calcium and/or phosphate and that these pass through the semipermeable membrane of the microcapsules, SmartCap Technology in effect creates an intra-capsular reservoir for this ion-rich aqueous solution.[39,45,49] The research discussed in this paper also proves that controlled ion release can be achieved by adjusting the microcapsule's shell, concentration of the aqueous solution, counterion, and dental material characteristics.[33-38] It may therefore be possible to control the long-duration ion release profile for a given ion/molecule and to optimize the desired clinical effect. In preventive products, including but not limited to fluoride varnishes and toothpastes, the ability to deliver fluoride, calcium and phosphate for caries control in a sustained and controlled manner using SmartCap Technology is advantageous, increasing the bioavailability of these ions. The ability to embed microcapsules into dental materials and products, including combinations of microcapsules containing different active agents, makes it possible to deliver these agents to the dentition or tooth-dental material interface.

SmartCap Technology offers significant opportunities beyond caries control and preventive products. Research on antimicrobial agents incorporated into microcapsules has demonstrated controlled release.[46,47] It can be envisioned that this provides a therapeutic opportunity with respect to preventing and treating periodontal disease. Further, it can be anticipated that other antimicrobial agents could also be utilized. Applications of antimicrobial SmartCap Technology can be envisioned with respect to periodontal disease, peri-implant disease and implant technologies, halitosis and other infections/conditions where control of bacteria is desirable.

The ability to incorporate microcapsules into restorative materials and cements provides several potential opportunities, based on the research: To help prevent the degradation of collagen fibrils in exposed demineralized dentin, by inhibiting matrix metalloproteinases (MMPs); to deliver calcium phosphate and fluoride to help prevent recurrent caries at the tooth-restorative material interface where microleakage and microfractures can occur; and, to alter the material properties by providing for autonomous self-healing of resin-based materials.[41,50-52] These uses of SmartCap Technology have the potential to extend the longevity and success rate of restorations. With respect to sealants, glaze materials and coatings, the controlled release of bioavailable fluoride, calcium and phosphate ions for extended periods of time, and ideally also between prophylactic examinations, could help control caries and/or deliver antimicrobials.

Conclusions

SmartCap Technology is a promising technology for the sustained, controlled release of anti-caries and antimicrobial agents from microcapsules embedded in dental products. While to date, the research has mainly focused on microcapsules delivering bioavailable fluoride, calcium and phosphate ions, the results of research on antimicrobial agents and self-healing agents in dental materials are also promising. Given the replenishment of these ions, the effect in dental materials would be ongoing while preserving the integrity of the material. Potential target applications for SmartCap Technology include but are not limited to dental sealants, restorative materials and cements, implant technologies, preventive products, oral first aid products and toothpastes.

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