Development of a Fluoridated, Daily-Use Toothpaste Containing NovaMin® Technology for the Treatment of Dentin Hypersensitivity

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Introduction

Calcium sodium phosphosilicate (trade name NovaMin®) is an inorganic amorphous compound that contains only calcium, sodium, phosphate, and silica. The calcium sodium phosphosilicate (CSPS) technology was invented by Professor Larry Hench at the University of Florida in the late 1960s, and found use in the development of new bone regenerative materials.¹ The original composition proposed by Professor Hench was the “45SS” composition, i.e., 45% SiO₂, 24.5% Na₂O, 24.5% CaO, and 6% P₂O₅ (in wt%). Anecdotally, this composition was selected to ensure that the Ca:P molar ratio was the same as hydroxyapatite in bone mineral.

The material was subsequently adapted for dentin remineralization during the mid-1990s by Drs. Leonard Litkowski and Gary Hack (both at the University of Maryland at that time), and Dr. David Greenspan.

In 2003, NovaMin Technology Inc. was formed to commercialize this novel compound. During the last 10 years, a range of professional and consumer products containing NovaMin were marketed. The first product developed by NovaMin Technology was a daily-use fluoride-free toothpaste containing 5% NovaMin (Oravive®). This product was approved by the US Food and Drug Administration (FDA) as a 510K medical device, indicated for the rapid and continual reduction of tooth sensitivity. NovaMin was subsequently formulated into over 15 products, including prophylaxis and regular toothpastes, and sold in more than 20 countries, including the USA, Canada, India, and China.

In 2010, NovaMin Technology Inc. was acquired by GlaxoSmithKline Consumer Healthcare (GSK). Recent GSK Oral Care research efforts have focused on the development of the first daily-use toothpaste for the treatment of dentin hypersensitivity containing 5% (in wt%) NovaMin and a source of fluoride.

This paper reviews the mode of action of NovaMin for the treatment of dental hypersensitivity, and discusses the development of a fluoridated daily-use toothpaste (Sensodyne® Repair and Protect, GlaxoSmithKline Consumer Healthcare, Weybridge, Surrey, UK) containing this technology. An overview of the other articles in this Special Issue, presenting technical and clinical efficacy results supporting this novel toothpaste formulation, is also presented.

NovaMin and Its Antisensitivity Mode of Action

The widely accepted theory for dentin hypersensitivity is the hydrodynamic theory developed by Brännström and Aström.² Fundamental to the premise of the hydrodynamic theory is the hypothesis that open dentin tubules allow fluid flow that excites the nerve endings in the dental pulp.

There are two basic approaches to the treatment of dentin hypersensitivity. The first is to treat the tooth with a nerve depolarizing agent, such as potassium nitrate, that penetrates into the dentin tubules and depolarizes the nerve synapse, thereby reducing sensitivity by preventing the conduction of pain impulses.³ The second approach is to treat the tooth with a chemical occluding agent, such as strontium chloride or acetate, which prevents fluid flow and therefore reduces tooth sensitivity.⁴ The mode of action of the NovaMin technology falls under the second approach, i.e., occlusion. Further NovaMin-related mechanistic detail is discussed below.

Research with NovaMin has shown that CSPS materials will form a strong attraction to collagen.⁵ ⁶ As dentin consists of a high proportion of collagen, it was proposed that NovaMin will bind to exposed dentin surfaces, as well as physically occlude dentin tubules. The interaction of NovaMin with collagen has been studied by several researchers using in vitro models. These studies have shown that the initial reactivity of the NovaMin particles is associated with the development of a surface negative charge, and that this enables binding to side groups on Type I collagen fibers.

When NovaMin particles come into contact with an aqueous environment such as water or saliva, an immediate release of sodium ions occurs which increases the local environmental pH. This combination of sodium ion release and pH rise facilitates the rapid precipitation of a calcium phosphate hydroxyapatite apatite layer following subsequent release of calcium and phosphate ions.⁷ Early in vitro studies⁸ demonstrated that NovaMin did, in fact, quickly occlude dentin tubules and form a protective layer on the dentin surface. Studies have shown that the CSPS particles can act as reservoirs to continuously release calcium and phosphate ions into the local environment.¹⁰

The role of soluble silica in the formation of the calcium phosphate mineral is also key. Damen and ten Cate studied the effect of soluble silica on the precipitation of calcium phosphates;¹¹ their research demonstrated that polymers of silicic acid increased the rate of precipitation of hydroxyapatite, even in the presence of inhibitors of hydroxyapatite. A feature of NovaMin particles is that they release silica into the local environment (at a concentration between 15 and 40 ppm); this is hypothesized to be one of the key enablers in the early stages of precipitation of calcium phosphate by providing a nucleating site. Computer modeling of the interactions of small silica chains with calcium and phosphate ions has shown that a three-member silica chain is optimal as a nucleating site for hydroxyapatite formation,¹¹ consistent with the mechanism of bioactive glasses proposed by Hench.¹
Development of a Fluoridated Daily-Use Toothpaste Containing 5% w/w NovaMin Technology

Since the 2010 post-acquisition phase of NovaMin technology, the GSK focus has been on developing a stable, esthetically pleasing, fluoridated, daily-use toothpaste containing 5% w/w NovaMin for the treatment of dentin hypersensitivity.

In order to protect the CSPS particles from reacting, it was necessary to formulate NovaMin in a non-aqueous, i.e., water-free formulation base. Given the calcium content of the particles, selection of an appropriate fluoride source was critical to ensure a stable product, and therefore sodium monofluorophosphate has been chosen, formulated to deliver 1450 ppm fluoride ion. Sensory research work identified a mint flavor which provided excellent base coverage and consumer-acceptable esthetics. This formulation, commercialized as Sensodyne® Repair and Protect, has been studied extensively in a body of in vitro, in situ, and clinical studies.

In the second article of this Special Issue, Earl, et al. describe work on the physical and chemical characterization of dentin surface effects following treatment with pure NovaMin and saliva substitutes. Use of modern imaging and analytical techniques demonstrated in vitro the reaction of the NovaMin material from amorphous calcium sodium phosphosilicate to crystalline hydroxyapatite. The occluding mode of action for the NovaMin technology was further confirmed via this work. Additional studies by Earl, et al. (third article of this issue), using a range of modern imaging and analysis techniques, have attempted to characterize in vitro the formation and substantivity of a layer formed on dentin following treatment with NovaMin when delivered as part of an anhydrous fluoridated toothpaste formulation. The results clearly demonstrate the NovaMin-containing formulation adheres to an exposed dentin surface. Characterization of the layer indicates that it is hydroxyapatite-like, and that the layer is resistant to acid and mechanical challenges.

In the fourth article of this Special Issue, Parkinson and Willson report on in vitro studies demonstrating that a fluoridated toothpaste containing 5% w/w NovaMin imparts significant tubule occlusion and dentin remineralization following four days of twice-daily brushing in the presence of an acid challenge. Surface analysis indicates that the occlusion and remineralization result from the formation of a calcium phosphate-enriched layer. Results from these studies support the proposed mode of action of NovaMin technology, and offer insights into differences in technical performance between toothpastes using chemistries with different mechanisms of action to generate tubule occlusion.

West, et al., in the fifth article of this issue, report the results of an in situ clinical study comparing the occluding properties of a toothpaste containing 5% w/w NovaMin and 1450 ppm F (as sodium monofluorophosphate) with a currently marketed toothpaste formulation containing 8% arginine/calcium carbonate, 1450 ppm sodium fluoride as fluoride ion (Colgate® Sensitive Pro-Relief™, Colgate-Palmolive Co., New York, NY, USA) on patent dentin tubules relative to negative controls of water and a non-occluding paste after four days of treatment with twice-daily brushing and a dietary acid challenge. Results confirm that the 1450 ppm sodium monofluorophosphate toothpaste with NovaMin demonstrated a statistically superior occluding effect on patent dentin tubules compared with water (p = 0.009) and a non-occluding control toothpaste (p = 0.02) at Day 4. In contrast, the 8% arginine/calcium carbonate toothpaste did not demonstrate the same degree of occlusive effect, showing no significant difference relative to the negative controls at the Day 4 time point. The results of this study provide further insights into the potential benefits of calcium sodium phosphosilicate to generate occlusion of patent dentin tubules in a more clinically relevant methodology.

In the sixth and final paper of this Special Issue, Gendreau, Barlow, and Mason summarize the clinical evidence for efficacy of NovaMin-containing toothpastes in the form of randomized, controlled clinical trials conducted in the USA, China, India, Thailand, and Ireland, supporting the effectiveness of toothpaste formulations containing 5% and 7.5% NovaMin for relief of pain from dentin hypersensitivity. Importantly, evidence from a non-inferiority design is described, supporting the bridging of clinical performance between proven fluoride-free toothpaste formulations containing 5% w/w NovaMin and the latest formulation combining this concentration of CSPS with a compatible source of fluoride, at 1450 ppm. These studies also show that anhydrous toothpaste formulations at concentrations of 5% and 7.5% NovaMin are well tolerated after extended treatment periods of twice-daily brushing.

In summary, the research outlined in this Special Issue of The Journal of Clinical Dentistry charts the development of the first fluoridated daily-use toothpaste containing NovaMin for the treatment of dentin hypersensitivity and repair of sensitive teeth. This product, based upon 5% w/w CSPS technology, has been shown to deliver a hydroxyapatite-like reparative layer to the surface of the dentin in vitro which is robust and resistant to acid challenge. In situ and clinical studies demonstrate the efficacy of this breakthrough formulation which is being commercialized in 2011 as Sensodyne Repair and Protect toothpaste.

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