Development of an antibacterial bioactive dental adhesive: Simplicity and innovation

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ABSTRACT: Purpose: Synthetic resins were originally used for esthetic purposes but have evolved as restorative materials. Achieving a strong, durable resin tooth adhesion has always been a topic of interest in the field of dentistry. This article demonstrates a review of a manufacturer's efforts to realize this goal through development of functional monomers since the 1970s. These functional monomers are thought to promote chemical adhesion to the dental substrate to prevent failure of restorations and to reduce the post-operative sensitivity. **Methods:** This review focuses on functional monomer with antibacterial properties to avert caries around restorations and improve durability of the bond. **Results:** This product is presented and discussed as bioactive adhesive. (*Am J Dent* 2018;31 (Sp Is B:13B-16B).

CLINICAL SIGNIFICANCE: Development of an antibacterial monomer that would polymerize and remain antibacterial over time can be clinically important to prevent secondary caries at the adhesive-tooth interface.

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Introduction

Dental caries is a multifactorial condition that results in cariogenic bacterial activity on the tooth surface destroying the dental tissue through acid production and enzymatic activity. Caries is considered to be a current oral health problem in many societies. In order to treat a decayed tooth, traditional dentistry used to eliminate the decayed tissue and healthy structure around it to create mechanical retention of predominantly metal-based materials for direct treatments. This was achieved through preparing a tapered box-shaped cavity, which could potentially result in excessive removal of sound tissues. Such excessive tissue removal would in turn result in structural weakness of the tooth. Leakage at the interface between restoration and tooth has been another frequent problem, which could lead to secondary caries, defined as demineralization of dental tissues around existing restorations. Bacteria would penetrate the dental structure through these interfacial defects. The lack of seal and bacterial leakage also resulted in other problems, such as increased risk of mechanical failure or dislodgement of the filling material and hypersensitivity of vital teeth, and patient discomfort after the treatment. Dentistry evolved with the introduction of adhesive dentistry, where resin-based materials could be bonded to the tooth. The bond was originally solely a "micro-mechanical" retention concept, achieved through acid-etching of the tooth to increase surface and available surface area, then a low-viscosity and hydrophobic resin diffused into enamel, whereby upon polymerization of the resin, adhesion was achieved to the enamel by interlocking of monomers into the enamel. However, bonding to dentin has proven to be more challenging, considering its inhomogeneous nature and high organic substance compared to enamel.

Our first total-etch bonding system was developed in the 1970s; "Clearfil Bond System" by Kuraray Co., Ltd.[a] (currently Kuraray Noritake Dental Inc.) based in Tokyo, Japan. In this polymer-based restorative system the phosphoric acid solution was applied to enamel and dentin simultaneously. Phenyl-P functional monomer was used as the adhesive resin monomer for this product, and indicated to apply phosphoric acid to both dentin and enamel, even when phosphoric acid etching to dentin had not been widely recognized internationally. The work to improve dental adhesives continued and Kuraray scientists incorporated an antibacterial adhesive property and developed a new monomer called methacryloyloxydodecylpyridinium bromide (MDPB), which was included in the primer of Clearfil SE Protect,[a] the two-step self-etch adhesive system. This approach can provide high chemical bond to the tooth substrate and eliminate any bacterial activity in the prepared cavity and prevent future microleakage. The formulation of MDPB and its mechanism of action will be further discussed.

Advancement of technology

Prior to the total-etching technique, the concept of acid etching was applied just to the enamel. It was only after the 1990s that the total etching system became well known and accepted in the world. Kuraray continued to improve technologies, since total-etching was an innovative method in which phosphoric acid was applied to both dentin and enamel simultaneously to prepare the tooth substrate for resin monomer penetration.

With earlier adhesives, post-operative sensitivity, secondary caries, and marginal discoloration were frequently reported. The gaps and clinical failures were likely caused by the low bond strength to tooth structure. Therefore, Kuraray developed a new original adhesive monomer "MDP," Methacryloyloxydecyl dihydrogen phosphate, in their adhesives, which achieved excellent adhesive bond strength. By incorporating MDP in their adhesives, long-term reliability and a very simple procedure were achieved.

The self-etch system was introduced from Kuraray first in 1993. It was Clearfil Liner Bond2[a] which had a mild pH and an adhesive monomer incorporated in a primer. Compared to the total-etching system, the enhanced self-etching system resulted in a reduced technique sensitivity since it has fewer steps and requires no rinsing or blot drying. Also, bonding with the self-etching showed much less postoperative sensitivity. Another clinically relevant issue was identified. In

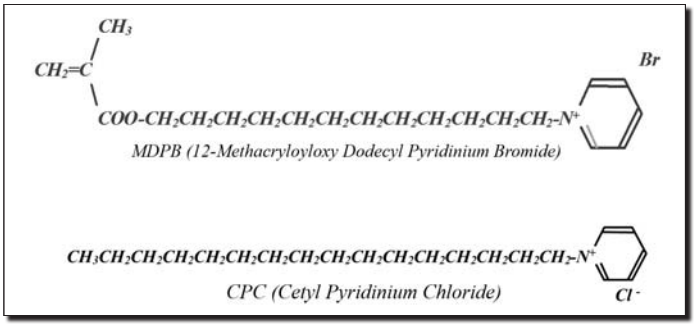

Fig. 1. Chemical structures of MDPB and CPC.

the total-etch technique, the acid etching often decalcifies dentin too deeply, which is deeper than the ability of bonding agents to penetrate. As a result, a discrepancy between decalcified dentin and penetrated bonding agent is created and appears as voids at the interface. These voids become a weak link in the technique. Kuraray continues to create adhesive technologies such as a catalyst system and patented purification process for MDP, which affects bond strength and durability.

"Minimum Intervention Dentistry" includes the careful and complete removal of caries-infected tooth structure. However, frequently diverse complications are encountered, where ideal treatment processes are sometimes difficult. For example, root caries adjacent to the gingiva are often extensive and extremely difficult to access with rotary instruments. Also, young patients with advanced carious lesions, where the dentist decides to stop before reaching the pulp tissue presents another challenging situation. Considering the many extraordinary complications that arise for complete removal of bacteria, Kuraray realized that something more than the conventional bonding systems are necessary. Although carious lesions occur as a result of multiple factors, caries is acknowledged by most scientists to be the result of bacterial infection of tooth structure. When a carious lesion is to be treated, basically the clinician removes all evident caries before restoring the tooth. However in spite of very careful treatment technique, clinicians often find caries adjacent to or under old restorations, possibly indicating the evidence of bacterial growth after the initial treatment procedure. It is difficult to determine if bacteria were inadvertently left, or they penetrated through gaps or microleakage over time. Therefore, the company scientists incorporated an antibacterial adhesive property and developed a new monomer called Methacryloyloxy Dodecyl Pyridinium Bromide (MDPB). MDPB incorporated in the primer is designed to work in the following way. First, any surviving bacteria in the cavity can be cleansed with the primer that includes the antibacterial monomer. Then the cavity walls and floor are completely sealed chemically with a very durable, high bond strength monomer, such as the adhesive monomer "MDP", which assures no microleakage thanks to the developed adhesive technologies. This was the first antibacterial adhesive as Clearfil Protect Bond (Clearfil Mega Bond FA[a] in Japan) in 2004, then the name later changed to Clearfil SE Protect[a] appealing to self-etch (SE) technology. The main components of the primer were MDPB, hydroxylethyl methacrylate (HEMA), dimethacrylate, and water. This product could target any potentiallysurviving bacteria in the superficial layer, then complete sealing of cavity floors and walls with a very durable high bond would be achieved, preventing the possible penetration of bacteria through microleakage, as the two main causes for secondary caries. The bonding system was registered as a Class III medical device in Japan and Europe, and in the US it was registered as 510(k) by the Food and Drug Administration (FDA). The developers also added sodium fluoride (as a fluoride releasing property) to the bonding agent. The main components of the bonding agent are MDP, HEMA, dimethacrylate, colloidal SiO_2 and an initiator. Fluoride would be present as MDP from the applied adhesive, and react with Ca from apatite and continues to be released into the tooth structure through a reaction with water inside the bonding layer.

Clearfil DC Activator[a] was added as an option for Clearfil SE Protect in 2014, indicated for core build-up and cementation with a dual-cured product. It is available to use for endodontically treated teeth, higher risk area when the bonding agent and this dual-cure activator are mixed. The activator contains a strong reductant, sufinate, which helps to cure the bonding agent with a dual cure composite, even under the acid condition.

What is MDPB?

MDPB is a compound of an antibacterial agent quaternary ammonium, methacryloyl group, and a designated antibacterial monomer (Fig. 1). This MDPB monomer has a formulation similar to the well-known antibacterial agent cetyl pyridinium chloride (CPC). CPC is used as the bactericide in toothpastes and mouth washes etc. This monomer has a very strong antibacterial property in the monomer compound and it is capable of destroying bacterial cell membranes as described above and it was believed the mechanism of antibacterial properties is same as that of CPC.

The action mechanism of MDPB is quite simple. The contact point for antibacterial effect is the pyridinium group, which has a positive charge. The bacterial cell membrane normally has a negative charge. Then when MDPB approaches the negatively charged bacteria, the negatively charged bacterial cell membrane is naturally drawn to the positive contact point of MDPB. Thus, the cell membrane loses its electrical balance and, as a result, the bacteria cell membrane is destroyed similar to a bursting soap bubble (a process called bacteriolysis) (Fig. 2). When the primer is applied to the cavity surface, MDPB diffuses and penetrates into the tooth structure. During the 20 seconds of priming time, MDPB acts against the bacteria and cleans the cavity surface.

Although MDPB has a similar chemical structure to CPC, it is enhanced by an additional and unique chemical structure. MDPB has a polymerization group at one end of the chain thus providing a point where it can be co-polymerized with another methacrylate compound when the visible light irradiates the bonding agent (Fig. 3).

The new bactericide with the polymerization group was also developed in consideration of maintaining antibacterial effect and antibiotics resistance issues. There are other types of antibacterial dental materials that include popular bactericides, such as clorhexidine or triclosan. However, those mate-

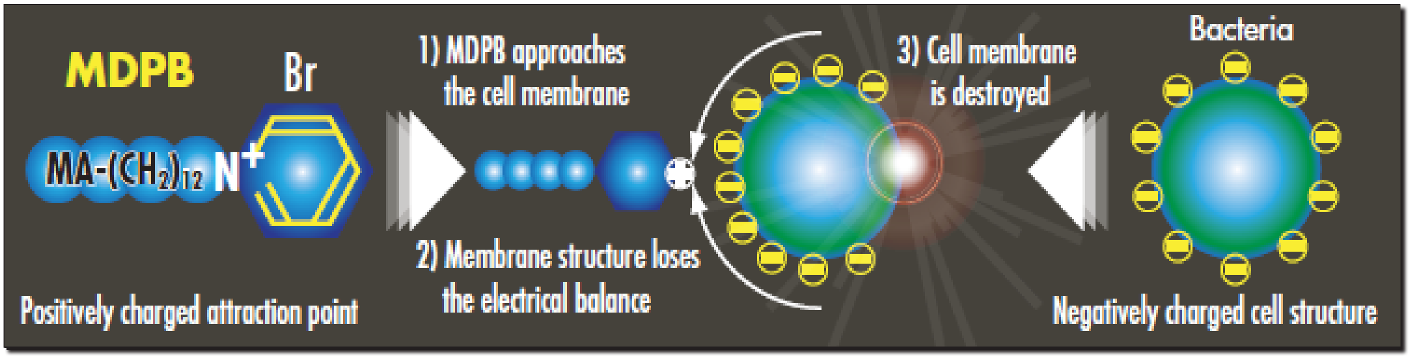

Fig. 2. Schematic antibacterial function of MDPB in three steps; (1) The positively charged MDPB molecule approaches the cell membrane; (2) The bacterial membrane structure loses the electrical balance; (3) The cell membrane is destroyed.

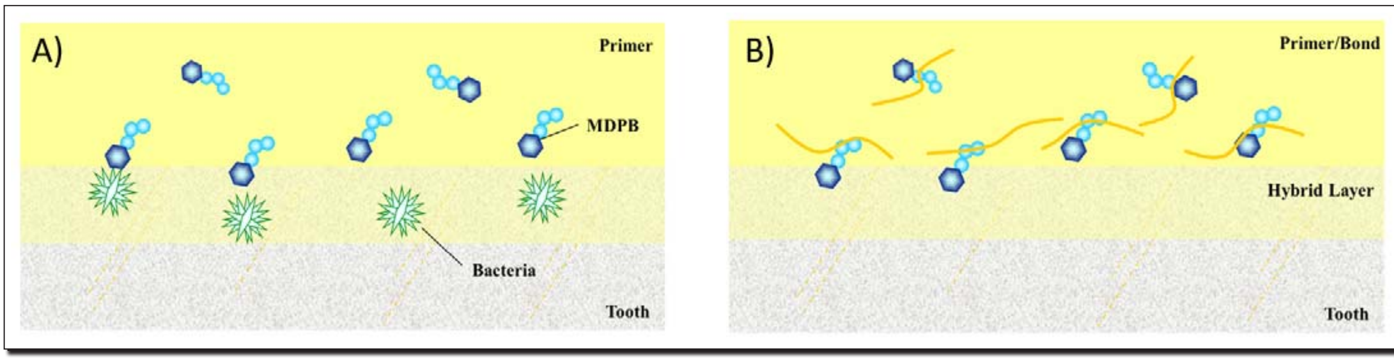

Fig. 3. Proposed functions of MDPB in the two-step self-etch adhesive; (**A**) When the primer is applied MDPS kills the remaining bacteria; (**B**) After polymerization of the adhesive, MDPB become a part of the bonding polymer layer and is immobilized in the resin matrix.

rials do not have any modifications to stop the continuous action of bacteria and release of the bactericide. Moreover, these bactericide materials will not polymerize with another monomer. Therefore, there is a risk of continuous dispersion into the oral cavity as well as the pulp tissue with its heavy vascular supply. Many scientists believe that continuous dispersion of a bactericide could result in the development of tolerance and resistance. Thus, MDPB was designed to prevent any dispersion of the bactericide after the restoration was cured and therefore, it is a very safe system.

Overview of research findings:

(1) Antibacterial properties of MDPB before polymerization - There are some research results for antibacterial properties against MDPB monomer and/or the product including MDPB, which are before polymerization of the monomer.

Antibacterial effects of MDPB monomer for various caries related bacteria were evaluated by Imazato et al.[1,2] They tested minimum bactericidal concentration (MBC) values for MDPB against a range of microorganisms detected in coronal caries lesions, including oral streptococci, lactobacilli, and a number of obligated anaerobic bacteria. The value range was from 15.6 to 125 µg/mL. It has been proven that MDPB has strong killing activity against various oral bacteria measured by its minimum bactericidal concentration values.

Antibacterial properties of the product including MDPB were evaluated by Turkun et al.[3] They investigated the properties of MDPB by the diameter of inhibition zone (millimeters) tested with agar well technique. In addition to that, they evaluated a number of recovered bacteria (CFU/ml) tested by the cavity model technique.[3] They compared that primer with the following three cavity disinfectants: chlorhexidine gluconate base, benzalkonium chloride based products, and 3% hydrogen peroxide. For cavity model technique, cylindrical cavities were prepared in the flat occlusal dentin of a human molar. The teeth were left in a broth culture of *Streptococcus mutans* allowing bacteria to invade, then tested materials were applied. After temporarily sealing and storing in saline, the dentin chips were collected and bacterial recovery was measured. Using the agar well technique, the MDPB-containing primer exhibited a greater inhibition zone than all three cavity disinfectants. When tested by the cavity method, the system showed significantly less bacterial recovery than all disinfectants. In addition, Imazato[4] reported similar results evaluating the inhibitory effects of seven commercially-available adhesives/primers against caries associated bacteria: *S mutans*, *L. casei* and *A. viscosus,* with the MDPB-containing primer showing more inhibition zones than the others.

Both articles concluded that the MDPB-containing system could inactivate the bacteria in the cavity more effectively than the tested cavity disinfectants or other adhesives.

(2) MDPB for long term durability - The immediate bond strength of contemporary adhesives is quite high, however, those bond strengths gradually weaken with aging, decreasing at rates of 35-40% in 6-12 months.[5-7] This is because of the degradation of the hybrid layer between resin adhesive and dentin interface.[1] Pashley et al[8] reported that endogenous matrix metalloproteinases (MMPs) bound to dentin contribute to the degradation of collagen fibrils in hybrid layers. The loss of collagen fibrils within the hybrid layer causes a loss of continuity with the underlying dentin, and decreases the bond strength to dentin. Therefore, they looked for compounds which were able to inhibit the activities of the enzyme.

Another study[9] revealed that the experimental 5 wt% MDPB, which is the same as the concentration of commercially available product, showed great inhibition of soluble recombinant human MMP-9 (rhMMP-9) and matrix-bound MMPs. Chlorhexidine is also reported as an anti-MMP compound, however, it is water-soluble and it does not have polymerizable functional groups in its chemical structure, meaning that it may reach out from its bonding interface. On the other hand, MDPB is polymerizable and it may work as an inhibitor for years. It can also be copolymerized and retained in the hybrid layer. Several studies have compared the durability of MDPB-containing adhesive systems to other adhesives. The reported results indicated improved long term durability in the MDPB-containing system compared to other adhesives in vivo and in vitro.[10,11] This may be partially explained by MDPB's anti-MMPs function.

(3) Clinical research results of the MDPB adhesive – A study[12] evaluating post-operative sensitivity of the adhesive system reported that no postoperative sensitivity was experienced at the 1-year evaluation period. The bonding system also showed excellent clinical performance in high stress bearing areas for at least 5 years.[13]

Conclusions

The incorporation of MDPB into the self-etching primer of the self-etching adhesive is a fine example of a marketed "bioactive adhesive". This new class of dental adhesives can do far more than simply bond to dentin. Such adhesives provide specific and robust function, inactivating residual bacteria in caries-infected dentin. They work for long term in the mouth to inhibit any endogenous MMPs that are activated by the caries process or that are exposed and activated by the self-etching adhesive system.

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Acknowledgements: To Dr. Alireza Sadr, Department of Restorative Dentistry, University of Washington, Seattle, Washington, for his advice on preparing this manuscript. The help of Selene Sarraf, University of Washington, Seattle, Washington, is appreciated in editing the text.

Disclosure statement: The author is an employee of Kuraray Noritake Dental Inc.

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