INTRODUCTION

Dental composites are commonly used restorative materials due mainly to their excellent esthetic and the substantial improvement of mechanical/physical properties of the materials. The major concern of the composite restorations is the failure from bacterial microleakage leading to secondary caries. The prevalence of secondary caries associated with dental composite was 3.6%1). Furthermore, 72% of the detected lesions required replacement which may inevitably lead to the further loss of tooth structure and compromise the strength of the restored tooth. The possible etiologies of secondary caries may be due to the errors during the complicated bonding procedures and the lack of remineralising and antibacterial actions of the materials2). The most frequently affected site was gingival floor in proximal restorations. This could be due to the leakage at deep cavity floor due to complicated placement technique or the suboptimal polymerization from limited light transmission or curing technique3). It was demonstrated that the release of unreacted monomers from the composites could promote the growth of cariogenic bacteria in dental biofilm2).

One of the strategies to develop the new composites is to simplify the restorative procedure to reduce the errors occurred during composite placement4). The development of self-adhesive dental composites (Vertise Flow, VF, Kerr, Orange, CA, USA) enabled rapid placement of materials without the need of complicated bonding procedures. VF consisted of adhesive monomers such as phosphoric-acid ester methacrylate and glycerol phosphate dimethacrylate (GPDM). The low pH of GPDM (pH~1.9) may enhance self-etching effect on tooth surface and promote hybrid layer formation between the composite and dentin5). Several studies however reported suboptimal bonding performance 6) and longevity of VF compared with conventional composites 7,8). This limitation could increase the risk of continue tooth demineralization and bacterial microleakage of the material.

Another proposed strategy to enhance the performance of composites is to enable remineralizing ability5,9). The addition of calcium phosphate (CaP) fillers encouraged the release of calcium and phosphate ions that enable the precipitation of mineral apatite on the surface of composites 10-12). The composites containing CaP also promoted remineralization of demineralized dentin13). The hydrophilic reactive fillers however inevitably reduced mechanical properties of the composites14).

Antibacterial agents have been added to dental composites to enhance antibacterial actions for composites. This may help prevent bacterial accumulation and microleakage at the tooth-composite interface. Chlorhexidine (CHX) is the most commonly used chemical for prevention and control of oral diseases. However, the drawbacks of CHX included low solubility, high toxic to human cells, and the risk to develop antibiotic resistance15,16). Furthermore, a rare but life threatening allergic reaction to CHX has also been reported17). Hence, an alternative antibacterial agent may be needed. Nisin is the subgroup of polycyclic peptide antibiotics, which was known as a lantibiotic. It consisted of 34-amino acids and exhibited amphipathic and cationic properties18). Nisin was produced by
**Lactobacillus Lactis** and has been approved by FDA as a food preservative\(^{19}\). Nisin also demonstrated antibacterial effects against oral microorganisms\(^{19,20}\) but it showed minimal toxic effects to human cells\(^{18,21}\). However, the commercial nisin usually contains NaCl. The incorporation of nisin into composites may therefore increase water sorption which may subsequently reduce physical/mechanical properties of the materials.

The aim of this study was therefore to develop self-adhesive and dual-cured dental composites with added MCPM and nisin. The effect of rising level of these additives on monomer conversion, biaxial flexural strength, and apatite forming ability of the composites was examined.

**MATERIALS AND METHODS**

**Composite preparation**

Two paste experimental composites were prepared using the powder to liquid ratio of 2:1. The initiator liquid (Table 1) consisted of urethane dimethacrylate (UDMA, Lot no. MKCG8230, Sigma Aldrich, St. Louis, MO, USA), triethyleneglycol dimethacrylate (TEGDMA, Lot no. STBF9549V, Sigma Aldrich), 2-hydroxyethyl methacrylate (HEMA, Lot no. STBG9652, Sigma Aldrich), 4-methacryloyloxyethyl trimellitic anhydride (4-META, Lot no. A766387 Polysciene, Warrington, PA, USA), camphorquinone (CQ, Lot no. 09003AQV, Sigma Aldrich), benzoyl peroxide (BP, Lot no. MKCF7091, Sigma Aldrich), and N, N-dimethyl-p-toluidine (DMPT, Lot no. MKBX9809V, Sigma Aldrich).

The composition of powder phase of each experimental composite is provided in Table 2. The powder phase consisted of silanated dental glass (33 wt% BaO, 50 wt% SiO\(_2\) and 9 wt% BO, Lot no. 806335, Esstech, Essington, PA, USA), monocalcium phosphate monohydrate (MCPM, Lot no. MCP-444950, Himed, Bethpage, NY, USA), and nisin Z (nisin, Lot no. 030220190415, Handary, Brussel, Belgium).

Powder and liquid phases were weighed and hand mixed using a plastic spatula. The mixed initiator and activator pastes were loaded into the double-barrel syringe and was injected using mixing tip and mixing gun (MIXPAC, Sulzer, Winterthur, Switzerland). Commercial self-adhesive dental composite (VF, Vertise flow, Kerr) was used as a comparison (Table 3)\(^5\).

**Monomer conversion**

An attenuated total reflection-Fourier transform IR (ATR-FTIR, Nicolet i5, Thermo Fisher Scientific, Waltham, MA, USA) was used to assess monomer conversion of the material (n=5). The composites were injected into the metal ring (1 mm in thickness and 10 mm in diameter) over the ATR diamond. The composites were covered with a clear acetate sheet. For assessing light activated polymerization, the composites were light cured for 40 s using an LED light curing unit (irradiance 1,250 mW/cm\(^2\), Demi Ultra, Kerr). The FTIR spectra at the region of 700–4,000 cm\(^{-1}\) of material prior and after curing were recorded. For the chemical activated polymerization, the composites were left cured on the ATR diamond for 10 min. Degree of monomer conversion (MC) of the composites was calculated using the following equation\(^{22}\).

\[
MC (%) = \frac{100 (B_0 - B_t)}{B_0}
\]

**Table 1** Composition of liquid phase

| Formulations | UDMA | TEGDMA | HEMA | 4-META | CQ | BP | DMPT |
|--------------|------|--------|------|--------|----|----|------|
| Initiator liquid (wt%) | 70 | 21 | 3 | 3 | 1 | 2 | 0 |
| Activator liquid (wt%) | 70 | 22 | 3 | 3 | 1 | 0 | 1 |

**Table 2** Composition of powder phase of the experimental composites

| Chemical/Formulations | M\(_4\)N\(_6\) | M\(_4\)N\(_3\) | M\(_6\)N\(_3\) | M\(_4\)N\(_8\) | M\(_6\)N\(_8\) |
|-----------------------|-------------|-------------|-------------|-------------|-------------|
| MCPM (M, wt%)          | 8           | 8           | 4           | 4           | 0           |
| Nisin (N, wt%)         | 6           | 3           | 6           | 3           | 0           |
| Dental glass (wt%)     | 86          | 89          | 90          | 93          | 100         |

**Table 3** Composition of the commercial material

| Name       | Lot no. | Composition | Supplier       |
|------------|---------|-------------|----------------|
| Vertise Flow (VF) | 6915030 | Resin: glycerolphosphoric acid dimethacrylate (GPDMA), HEMA, bisphenol glycidil dimethacrylate (Bis-GMA), catalysts | Kerr, Orange, CA, USA |
|            |         | Fillers: pre-polymerized filler, silanated barium glass, nano-sized colloidal SiO\(_2\), YF\(_3\) (70 wt%) |                |
Where $B_0$ and $B_t$ were the absorbance of the C-O peak (1,320 cm$^{-1}$) above background level at 1,335 cm$^{-1}$ initially and after time $t$\textsuperscript{19}.

**Biaxial flexural strength (BFS) and biaxial flexural modulus (BFM)**

Disc specimens were prepared by injecting the materials into a metal circlip (1 mm in thickness and 10 mm in diameter, $n=6$). The specimens were covered with an acetate sheet and light cured for 40 s on top and bottom surfaces. They were left at room temperature for 24 h. Then, they were removed and immersed in a tube containing 10 mL of deionized water and incubated at 37 °C for 24 h and 4 weeks. Prior the test, specimen’s thickness was measured using a digital vernier caliper. The discs were then placed on the ball-on-ring testing jig under the mechanical testing frame (AGSX, Shimadzu, Kyoto, Japan). The test was performed using 500 N load cell with a crosshead speed of 1 mm/min. BFS (Pa) was calculated using the following equation\textsuperscript{20}.

$$\text{BFS}=\frac{F}{A}\{1+(\frac{0.485}{\ln(\frac{r}{r_0})+0.52)}\}+0.48\} \quad \text{Equation 2}$$

Where $F$ is the load at failure (N), $d$ is the specimen’s thickness (m), $v$ is Poisson’s ratio (0.3). Additionally, BFM was calculated using the following equation\textsuperscript{20}.

$$\text{BFM}=(\frac{\Delta H}{\Delta W_e})\times(\frac{B_0d^2}{q^2}) \quad \text{Equation 3}$$

Where $\frac{\Delta H}{\Delta W_e}$ is the rate of change of load with regards to central deflection or gradient of force versus displacement curve (N/m), $B_0$ is center deflection junction (0.5024)\textsuperscript{24}, $q$ is ratio of support radius to the radius of disc. Additionally, the fracture surface of tested specimens was examined under a scanning electron microscope (SEM, JSM 7800F, JEOL, Tokyo, Japan).

**Shear bond strength (SBS)**

The ethical approval for collecting extracted teeth was granted from Thammasat University Ethical Committee (ID 167/2562). Forty-eight extracted and caries free human third molars were collected and stored in 1% thymol solution for 2–4 weeks prior the test. Teeth were embedded in self-cured acrylic resin and stored in 1% thymol solution for 2–4 weeks prior the test\textsuperscript{25}. The macro SBS testing was performed using a SBS testing jig under a mechanical testing frame using 50 N load cell and the crosshead speed of 0.5 mm/min. SBS (Pa) was calculated using the following equation.

$$\text{SBS}=\frac{F}{A} \quad \text{Equation 4}$$

Where $F$ is the load at failure (N) and $A$ is the area of bonding interface (mm$^2$). The failure mode at the tooth-composite interface was analyzed under a stereomicroscope.

**Surface apatite formation**

Disc specimens were prepared ($n=1$) and immersed in 10 mL simulated body fluid (SBF) prepared according to ISO BS ISO 23317:2014\textsuperscript{26}. The specimens were incubated at 37 °C for 4 weeks. Then, they were removed, blotted dry, and sputter coated. The surface apatite was examined using an SEM equipped with Energy Dispersive X-ray (EDX, Inca X-sight 6650 detector, Oxford Instruments, Abingdon, UK)\textsuperscript{10,11}.

**Statistical analysis**

Values reported in the current study are mean±SD. The data were analyzed using Prism 8 (GraphPad Software, San Diego, CA, USA). Normality of the data was initially verified using the Shapiro-Wilk test. The results indicated that only data from chemical-activated monomer conversion were not normally distributed. For normally distributed data, One-way ANOVA followed by post-hoc Tukey multiple comparison was used to analyze the result. For non-normally distributed data Kruskal-Wallis test followed by Dunn’s multiple comparison was employed. Significance level was set at $p=0.05$. Additionally, post-hoc power analysis was performed using G*Power 3.1 Software (University of Dusseldorf, Germany)\textsuperscript{27}. The effect size (Cohen’s $f$) used in the G-Power software was calculated using the following equation.

$$\text{Cohen’s } f = \sqrt{\frac{\sum_{i=1}^{n}(\mu_i-\mu)^2}{p}} \quad \text{Equation 5}$$

Where $\mu$ is mean, $\sigma$ is common SD, and $p$ is the number of groups which can be obtained from the results. The methods for sample size and power calculations using the software were explained in detail in the published studies\textsuperscript{28,29}. The results confirmed that the sample size of each test gave power $>0.99$ at $a=0.05$. Furthermore, factorial analysis\textsuperscript{10} was employed to assess the effect of rising level of MCPPM and nisin on properties of the composites.

**RESULTS**

**Monomer conversion**

For light activated polymerization, the highest mean monomer conversion was observed with M0N0 (75.8±1.6%) followed by M8N6 (73.9±1.7%), M4N3
Fig. 1  A) Degree of monomer conversion upon light and B) chemical activation. The boxes represent the first quartile (Q1) to the third quartile (Q3), the horizontal lines in the box represent the median, the whiskers represent the maximum and minimum values, and “+” represents the mean value (n=5). Lines with the number indicated significant differences with \( p \) values.

Fig. 2  Biaxial flexural strength and modulus of elasticity after the immersion in deionized water for 24 h (A, C) and 4 weeks (B, D). The boxes represent the first quartile (Q1) to the third quartile (Q3), the horizontal lines in the box represent the median, the whiskers represent the maximum and minimum values, and “+” represents the mean value (n=6). Lines with the number indicated significant differences and \( p \) values. E) Fracture surface of the tested sample revealed apatite-like crystals precipitated in the core (arrow).
The conversions of experimental composites were significantly higher than that of VF (65.6±1.5%). Additionally, M0N0 showed significant higher conversion than M8N3. The average conversion obtained from chemical-activated polymerization (~59.2%) was lower than that of the light-cured polymerization (~73.7%). The highest mean conversion from chemical-activated polymerization was obtained from M8N6 (60.0±2.7%) followed by M0N0 (59.4±1.0%), M8N3 (59.2±4.9%), M8N6 (59.1±3.8%), and M4N3 (57.9±3.0%). However, no significant difference was detected amongst the materials. The addition of MCPM and nisin showed negligible effect on the conversion of experimental composites.

**BFS and BFM**

At 24 h, the highest and lowest BFS were obtained from M0N0 (216±14 MPa) and M8N6 (133±14 MPa) respectively (Fig. 2). VF exhibited comparable BFS (178±27 MP) to M0N0, M8N3 (149±21 MPa), M4N6 (154±18 MPa), and M4N3 (173±19 MPa). The BFM of M0N0 (5.7±0.4 GPa) was comparable to that of M8N3 (5.1±0.2 GPa), M6N4 (5.3±0.3 GPa), and M4N3 (4.3±0.3 GPa). Furthermore, VF showed comparable BFM (5.7±0.4 GPa) to M8N6 (4.1±0.4 GPa). Factorial analysis indicated that rising level of MCPM and nisin reduced BFS by 17±14% and 13±8% respectively. Additionally, rising MCPM and nisin reduced BFM by 18±12% and 12±7% respectively.

BFS and BFM of all materials were decreased upon immersion in water. The lowest BFS at 4 weeks was observed with M8N6 (86±26 MPa) which was comparable to that of VF (115±10 MPa). Rising the level of MCPM and nisin reduced BFS by 30±23% and 25±20% respectively. Furthermore, fracture surface of the tested specimens revealed the precipitation of dicalcium phosphates in the core of materials. Results from EDX showed that Ca/P atomic ratio of the apatite-like crystals was ~1.05.

**SBS to dentin**

VF showed the highest SBS (13±7 MPa) which was significantly higher than all experimental composites
polymer10,34). The level of additives used in this study was selected due mainly to the increase of light scattering due to the lower monomer conversion of the composites when compared to the base monomer. It is demonstrated that the use of low glass transition temperature monomers (UDMA=−8°C) could promote high degree of monomer conversion for the polymer20,31).

The addition of BP in initiator paste and DMPT in the activator paste enabled chemical activated polymerization for the composites. This is expected to help ensure optimal polymerization at the bottom of deep cavity where the light transmission may be limited. Although the conversion upon chemical activation was lower than that observed with light activation, the values were still in the range (60%) observed with conventional composites (~40–75%)32). Furthermore, it was demonstrated that composites that exhibited monomer conversion greater than 50% showed minimal amount of eluted monomers33). The previous studies demonstrated that the addition of reactive fillers (up to 20 wt%) reduced monomer conversion of the composites due mainly to the increase of light scattering due to the refractive indices mismatch between fillers and polymer10,34). The level of additives used in this study (up to 14 wt%) seem to exhibit negligible effect on the conversion of composites. However, the conversion in the current study was measured at the specimen’s thickness of 1 mm. In the future studies, the conversion will be tested at greater thickness as the cavity depth can be up to 3–5 mm35).

BFS and BFM
Flexural test is a common test to characterize the strength of dental composites. Currently, the BS EN ISO 4049:2019 Dentistry: Polymer-based restorative materials requires flexural strength of at least 80 MPa from 3-point bending test at 24 h for dental composite restorative materials36). BFS test was employed in the current study as the test showed similar but higher reproducibility results compared to 3-point bending test37). The results from the current study also suggest that the materials could pass the requirement.

The strength of the composites was decreased upon the addition of MCPM and nisin. These additives may promote water sorption that could plasticize the resin matrix and mechanical affect the strength of materials38). However, the strength obtained from the current study (133–216 MPa) was comparable or higher than that reported from dental composites containing CaP fillers in published studies (60–100 MPa39), 104–154 MPa40), 105–120 MPa41), 188–165 MPa42). Additionally, the fracture surface of composites (Fig. 2) revealed the formation of apatite-like phase in the core of the specimen. It was expected that the crystal could be dicalcium phosphates (Ca/P ~1.00, brushite or monetite)43). The formation of the apatite-like phase may help fill defects or voids in the core which could potentially help retard crack propagation44).

SBS
The placement of dental composites requires multiple steps and highly technique sensitive dentin bonding procedure. The error during placement could lead to suboptimal performance of the material or bacterial microleakage. The self-adhesive composites were developed which could facilitate placement without the need for etching or bonding protocols prior the composite placement. In vitro studies however revealed limited interaction between self-adhesive composites to tooth45,46).

It is expected that rising level of acidic and hydrophilic fillers such as MCPM may help promote self-etching properties and wettability to enhance composite-dentin interaction without using adhesive. However, the result suggested that effect of MCPM on SBS was negligible. SBS of VF was higher than that of the commercial materials. During placement, the apparent viscosity of VF was lower than the experimental composites. This may suggest that VF contained higher level of adhesion promoting monomer, such as HEMA, that help increase wettability to the tooth surface for VF. Furthermore, 4-META (pH~3–4) may not be able to etch tooth surface efficiently compared to GPDM (pH~2) contained in VF47). This ultra-mild etching ability of 4-META in experimental composites may then limit the interaction and bond strength between the composites and dentin48). Future works need to assess the difference between using different type of acidic monomer to optimize the formulation.

Surface apatite formation
The ability of materials to enable surface apatite formation after immersion in SBF is a feasible technique to preliminary examine the remineralizing ability of materials to prevent microleakage. It is postulated that the addition of BP in initiator paste and DMPT in the activator paste enabled chemical activated polymerization for the composites. This is expected to help ensure optimal polymerization at the bottom of deep cavity where the light transmission may be limited. Although the conversion upon chemical activation was lower than that observed with light activation, the values were still in the range (60%) observed with conventional composites (~40–75%)32). Furthermore, it was demonstrated that composites that exhibited monomer conversion greater than 50% showed minimal amount of eluted monomers33). The previous studies demonstrated that the addition of reactive fillers (up to 20 wt%) reduced monomer conversion of the composites due mainly to the increase of light scattering due to the refractive indices mismatch between fillers and polymer10,34). The level of additives used in this study (up to 14 wt%) seem to exhibit negligible effect on the conversion of composites. However, the conversion in the current study was measured at the specimen’s thickness of 1 mm. In the future studies, the conversion will be tested at greater thickness as the cavity depth can be up to 3–5 mm35).
the composites$^{40}$. In general, water solubility of CaP decreases upon the increase of Ca/P ratio$^{40}$. Tricalcium phosphate (TCP, particle diameter of 4 µm) was used as the remineralizing agent in the pilot study but it failed to encourage surface apatite precipitation. This could be due to the limited water solubility of TCP (Ca/P ratio=1.5). The current study therefore used higher soluble MCPM (Ca/P ratio=0.5) as the filler phase, which enabled apatite-like CaP crystals precipitated on the surface. The apatite-like crystals were expected to be calcium deficient-hydroxyapatite (Ca/P ratio=1.67)$^{40,43}$. It can be seen that the apatite-like crystals were more clearly observed when the level of MCPM was increased to 8 wt%. EDX results also suggested that the crystals could be calcium-deficient apatite which was commonly found in human hard tissues. A previous study demonstrated that the composites that can promote surface apatite formation could enable in vitro dentin remineralization$^{46}$. The ability of composites to encourage surface apatite may suggest that the materials could help remineralize the demineralized dentin$^{46}$.

**CONCLUSION**

The experimental dual-cured and self-adhesive composites containing MCPM and nisin were developed. The monomer conversion upon light curing of the experimental composites was higher than that of the commercial material. The flexural strength of composites at 24 h was comparable or higher than that of VF. The composites showed lower SBS than VF. Rising level of MCPM promoted apatite-like crystals formation on the surface of experimental composites. Rising level of MCPM and nisin showed no detrimental effect on the conversion and SBS of the experimental composites. The additives however reduced the strength of the composites but the values were still in the acceptable range required by the ISO standard.

**CONFLICT OF INTEREST**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**ACKNOWLEDGMENTS**

This study was supported by Thammasat University Research Fund (Contract No. TUGT 3/2562). The authors would like to thank Thammasat University Center of Scientific Equipment for Advanced Research (TUCSEAR) for providing technical supports. The authors also thank Sulzer for supporting syringes and mixing tips (MIXPAC).

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