INTRODUCTION

Polymethyl methacrylate (PMMA) resin has long been used in biomaterials including dental restorative materials and an orthopedic bone-cements\textsuperscript{1-6).\textsuperscript{1} Most of these materials are fabricated by polymerizing a mixture of methyl methacrylate (MMA) and PMMA powders with a polymerization initiator\textsuperscript{7-9). Benzoyl peroxide (BPO) and 2,2´-azobisisobutyronitrile (AIBN) are commonly used as thermal radical polymerization initiators. However, in biomaterials used directly in the human body, the polymerization at high temperature in the body is not suitable. Therefore, the redox polymerization initiator of BPO with aromatic tertiary amines (BPO/amine) and partially oxidized tri-n-butylborane (TBBO) that can polymerize at room temperature have become popular. Particularly, trialkylborane has been used as an excellent initiator for grafting MMA to collagen, silk threads, and low-surface-energy resins\textsuperscript{10-12). Because TBBO is less sensitive to air and water during polymerization\textsuperscript{13}, MMA can be polymerized under moist oral conditions and yields high bond strength of the tooth structure\textsuperscript{14,15). Hirabayashi and Imai reported MMA polymerization in the presence of PMMA powder using TBBO or BPO/amine at body temperature (37°C) and found that the temporal change of the residual MMA significantly differed among the two initiators. The residual MMA at 30 min, 24 h as well as 1 and 4 weeks decreased from 8.39 to 4.50, 3.67, and 3.54\%, respectively for BPO/amine, and from 8.15 to 1.96, 0.84, and 0.48\%, respectively, for TBBO\textsuperscript{16). The weight-averaged molecular weight ($M_w$) of PMMA produced with the BPO/amine system decreased from $2.97\times10^5$ to $2.35\times10^5$ between 30 min and 24 h, then increased to $2.82\times10^5$ after 4 weeks. For the TBBO system, $M_w$ decreased significantly from $4.09\times10^5$ to $2.47\times10^5$ between 30 min and 4 weeks\textsuperscript{16,17). These studies showed that TBBO exhibits unique performance as a radical polymerization initiator, completely different from BPO/amine.

Although biocompatibility is important for biomaterials, detrimental effects to the surrounding tissues due to the residual monomers eluted from the polymerized resin is another major problem\textsuperscript{18-20). Interestingly, dental resin prepared using TBBO initiator exhibited minimal cytotoxicity when the polymerized materials were used\textsuperscript{21), excellent biocompatibility with periodontal tissues compared to other dental materials\textsuperscript{22}, and ability to directly contact bone without inflammation\textsuperscript{23). Although TBBO-initiated MMA polymerization exhibits unique polymerization behavior, its mechanism has not been sufficiently studied. Therefore, the purpose of this study was to investigate the precise behavior of MMA polymerization initiated by TBBO by comparing it with the BPO/amine initiator which is commonly used in dental materials.

MATERIALS AND METHODS

**Materials**

MMA (Mitsubishi Rayon, Tokyo, Japan), stabilized with 50 ppm of hydroquinone, was used without further purification. TBBO and PMMA powders (mean particle
Table 1 Codes and compositions of the resins studied

| Resin code  | Composition (mass %) |
|------------|----------------------|
|            | TBBO  | BPO  | DMPT |
| TBBO       | 7.2   | —    | —    |
| BPO/amine  | —     | 1.0  | 0.2  |

TBBO: partially oxidized tri-n-butylborane, BPO: Benzoyl peroxide, DMPT: N,N-Dimethyl-p-toluidine

Comparison of TBBO and BPO/amine for MMA polymerization

1. Specimen preparation
The TBBO specimen was obtained by adding 7.2 wt% TBBO to MMA. The BPO specimen was prepared as follows: 2.0 wt% BPO and 0.4 wt% DMPT were added to the MMA individually, and equal amounts of both monomers were mixed. The mixture was subsequently stored in a 37°C thermostatic chamber for 30 min after sample preparation. The residual MMA in the specimens after 30 min to 3 h and the molecular weight after 3 h were measured (n=3). The sample codes and compositions are listed in Table 1.

2. Measurement of residual MMA
Residual MMA was measured using high performance liquid chromatography (HPLC, LC-20AD, Shimadzu, Kyoto, Japan) equipped with a column (Inertsil ODS-3, 4.6 mm I.D. ×150 mm, GL Sciences, Tokyo, Japan) and a diode detector (SPD M20A). The polymerization resin (40 mg) was dissolved in 2.5 mL of acetone (Wako Pure Chemical Industries, Osaka, Japan), and 5 mL of methanol (Wako Pure Chemical Industries) was subsequently added to the solution to precipitate the polymer. The supernatant of the solution was filtered through a 0.20 μm pore size filter (Toyo Roshi Kaisha, Tokyo, Japan). Reversed-phase HPLC analysis was performed using a 240 nm detection wavelength. The sample solution (5 μL) was injected and analyzed at 40°C at a 1.0 mL/min flow rate. The mobile phase consisted of acetonitrile and 0.1% trifluoroacetic acid solution (mixing ratio 50:50). The proportion of MMA in the entire polymerization resin was calculated as the residual MMA ratio (%).

3. Measurement of molecular weight
Molecular weight of the polymerized resin was measured by size exclusion chromatography (SEC). The polymerized resin was dissolved in tetrahydrofuran (THF, Wako Pure Chemical Industries) and the solution was filtered using a 0.45 μm pore size membrane filter (Toyo Roshi Kaisha). The filtrate was measured using a GPC system (LC-10ADvp, Shimadzu) with an 8 mm I.D. ×300 mm GPC column (LF-804, SHOWA DENKO) at 40°C using THF as an eluent at a flow rate of 1.0 mL/min. The number-averaged ($M_n$) and weight-averaged ($M_w$) molecular weights were calculated using the calibration curve of the PMMA standard.

Fig. 1 Representative ESR spectrum of the polymerization radicals of MMA.

Observation of electron spin resonance (ESR) spectrum and measurement of radical intensity by spin trapping method

1. Preparation of specimens
The specimens were fabricated by mixing an equal weight of PMMA powder and MMA liquid. The PMMA powder was used for the TBBO polymerization system, and PMMA with 1.0 wt% BPO was used for the BPO/amine system. TBBO (7.2 wt% to MMA) was added right before mixing the powder and liquid. PMMA containing 1.0 wt% BPO was mixed with MMA with 0.2 wt% DMPT for the BPO/amine system.

2. Measurement of ESR spectrum
Approximately 0.2 g of the powder/liquid mixture was immediately filled in a CR syringe (Centrix, Shelton, CT, USA) and injected into a 2 mm I.D. ×2.5 mm Teflon tube (Chukoh Chemical Industries, Tokyo, Japan). The reaction time was counted starting from the moment of contact to the mixture. The specimen in the Teflon tube was inserted to the ESR sample tube (NEW Era Enterprises, Vineland, NJ, USA) and then the radical...
intensity of the specimen was measured by the ESR device (JES-FR30, JEOL, Tokyo, Japan). The ESR parameters were: 4.00 mW microwave power, 337.442 mT center field, 25 mT sweep width, 0.5 min sweep time, 0.5 mT modulation width, 100 amplitude, and 0.03 s time constant. The ESR measurements were performed at 37°C.

As shown in Fig. 1, the spectrum intensity of Mg²⁺ thermally diffused into MgO was used as a marker spectrum, and the radical intensity was calculated from the relative intensity of the MMA-derived ESR spectrum normalized to the marker spectrum.

Polymerization reaction of MMA in the presence of polymers initiated with TBBO or BPO/amine

PMMAs polymerized using TBBO and BPO/amine systems were used. The polymers were obtained by storing the respective PMMA/MMA mixture in a 37°C thermostatic chamber for 72 h. The obtained polymers were cut into small pieces (approximately 2 mm by 2 mm), and 1.0 g of the polymer fragments were added to 2.0 g of MMA and stirred until the fragments were completely dissolved. After fragment dissolution, the specimens were stored in the 37°C thermostatic chamber for 24 h. Residual MMA in the specimen was quantified by HPLC according to the aforementioned conditions (n=7). A control specimen where the fragment did not include TBBO or BPO/amine was also prepared.

RESULTS AND DISCUSSION

PMMA resin dental material was prepared by the radical polymerization of the mixture of MMA liquid and PMMA powder using radical polymerization initiators. Polymerization of MMA can be accelerated by the gel effect due to the addition of PMMA, so the setting time required to form the biomaterial was adjusted appropriately. However, at the beginning of this study, the residual MMA and molecular weight of the produced PMMA were measured without PMMA powder addition to precisely compare the polymerization performance of MMA initiated by TBBO with that of the BPO/amine system.

The residual MMA at representative time points is shown in Fig. 2. It was confirmed that no volatilization occurred under the polymerization condition used herein. A blank experiment of polymerization under the same reaction condition without initiator showed no weight loss during polymerization. As a result of the bulk polymerization of MMA at 37°C using TBBO, the residual MMA in the product decreased to 74% after 30 min, then drastically declined to fully consume the MMA after 3 h. Meanwhile, although the residual MMA in the BPO/amine polymerization after 30 min was similar to that of the TBBO-initiated polymerization, no further polymerization occurred afterwards.

The molecular weights of the polymer specimens after 3 h of polymerization are listed in Table 2. The molecular weights of the polymers obtained using TBBO were more than twice as high as that of those obtained using BPO/amine. In addition, in the BPO/amine system, no polymerization occurred after 30 min of reaction time. This suggested that the radicals were inactivated by termination reactions in less than 30 min in BPO/amine system. Typical lifetimes of growing species in radical reactions are on the order of a few of seconds. Similarly, the reaction of the BPO/amine system finished in less than 30 min. However, the TBBO system showed
different process characteristics. The polymerization reaction of the TBBO system rapidly proceeded and consumed the MMA monomer within 3 h. This indicates that the activity of the growing species generated with TBBO was maintained over a longer period compared to that of the BPO/amine system.

The ESR of the TBBO and BPO/amine systems was also examined. Polymeric dental materials are generally fabricated using the radical polymerization process, and ESR analysis of the polymerization process has revealed important mechanistic information. ESR analysis can instantaneously measure the radical intensity in the polymerizing sample, therefore, ESR samples were prepared under the same condition used in clinical dentistry, namely PMMA powder was mixed with MMA and polymerization initiators. MMA polymerization for dental use typically involves additional PMMA powder. A paste like mixture of MMA and PMMA powder is commonly used for polymerization to form resins. The ESR radical intensity generated during the polymerization of MMA by TBBO and BPO/amine are shown in Fig. 3. Differences in the relationship between radical intensity and reaction time was clear between the TBBO and BPO/amine systems. In the TBBO system, radical intensity gently increased during the first 20 min of the reaction. The intensity reached a maximum

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**Table 2** Molecular weight of the polymethylmethacrylate prepared by TBBO and BPO/amine initiator systems

| Resin code | $M_n$ ($\times10^3$) | $M_w$ ($\times10^3$) | $M_w/M_n$ |
|------------|----------------------|----------------------|-----------|
| TBBO       | 93 (4.5)             | 249 (69)             | 2.7 (0.7) |
| BPO/amine  | 44 (1.9)             | 90 (4.6)             | 2.1 (0.1) |

$M_n$: The number-averaged molecular weight, $M_w$: The weight-averaged molecular weight After 3 h polymerization. Mean (SD)

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**Table 3** Conversion of MMA by the polymer fragments that were initiated with TBBO or BPO/amine

| Resin code | Conversion rate of MMA (%) |
|------------|----------------------------|
| TBBO       | 29.8 (8.9)                 |
| BPO/amine  | -0.3 (2.4)                 |

After 24 h polymerization. Mean (SD)
at 10 days and was maintained for more than 3 months. For the BPO/amine system, the radical intensity sharply increased from 5 to 30 min and subsequently decreased. The radical intensity was hardly detected after 50 h, which was consistent with residual MMA found in bulk polymerization by TBBO and BPO/amine.

Based on the above findings, the polymerization reaction of MMA with the polymer fragments obtained after 72 h were further examined. The radical intensity in the TBBO system reached a maximum, whereas the radical intensity in the polymer fragments with BPO/amine was inactivate. The results of the conversion rates of MMA including the polymer fragments are listed in Table 3. MMA polymerization did not proceed in the presence of polymer fragments with BPO/amine, whereas in the TBBO system, the conversion of MMA was approximately 30% after 24 h of polymerization. This indicated that the polymer fragments polymerized by TBBO still possessed polymerizability. It is likely that the polymerization reaction using TBBO proceeds by reaction with oxygen in the sample, then free radicals in the polymer are maintained in a frozen state as the sample viscosity increased until it solidified. However, the free radicals retained in the polymer could be reactivated by the polymer liquefying in the presence of MMA monomer, thereby facilitating the further polymerization of MMA.

Compared to the normal radical reactions, TBBO system showed exceptionally longer lifetime of the free radical species.

Numerous studies have been performed regarding the radical generation mechanism of trialkylborane\(^{29-31}\). It was reported that the radical generating source is a trialkylborane oxide, and that the polymerization of monomers does not proceed without oxygen. Chung et al.\(^{32}\) reported that alkylboranes such as triethylborane could function as a living polymerization initiator for styrene and methacrylic acid esters in the presence of oxygen. Taira and Imai\(^{15}\) reported the reaction mechanism in the polymerization of MMA by TBBO shown in Fig. 4. Initially, a high-molecular weight polymer was formed, composed of TBBO and the polymer radical generated in the early stages of polymerization. The polymer radical initiated with TBBO was oxidized by oxygen, generating polymer peroxides. During these processes oxygen was gradually consumed, allowing the polymer radicals to remain active for a long period of time. Although these polymer peroxides were stable, chain transfer reactions

![Fig. 4](image)

**Fig. 4** Previously reported mechanism of MMA polymerization by TBBO\(^{32}\).

![Fig. 5](image)

**Fig. 5** Comparison of the molecular-weight-distribution curves after 3 h of polymerization for the (A) TBBO, (B) BPO/amine specimens. Experiments were performed in triplcate \(n=3\) (Sample No. 1: black, No. 2: pink, No. 3: blue).
with the polymer radicals could easily occur. When a peroxide bond in the polymer was fragmented by a chain transfer reaction, its molecular weight decreased.

The molecular-weight-distribution curves in Fig. 5 showed that the PMMA obtained using the BPO/amine system exhibited a reproducible and unimodal distribution curve, whereas the PMMA obtained using the TBBO system exhibited deviations in its GPC traces and one of the three specimens showed a bimodal distribution curve. This result is consistent with the mechanism reported by Taira and Imai. Subsequently, Muraki et al. proposed that methoxydiethylborane and 9-borabicyclo[3.3.1]nonane can function as a living radical polymerization initiator and suppress the disproportionation reaction by forming dormant species. In their study, polymerization occurred in the absence of oxygen, so herein all specimens were kept sealed after the preparation. Thus, it was speculated that the reactions proceeded in absence of oxygen, since all dissolved oxygen during specimen preparation was consumed. Assuming that the polymerization progressed without oxygen, it is possible that the TBBO used in this study functions as a controlled radical polymerization initiator for MMA.

In ordinary radical polymerizations, termination reactions such as bimolecular termination and disproportionation occur then the typical lifetime of growing species reaction is on the order of a few seconds. However, the TBBO system used in this study was effective for the polymerization of MMA and the radical intensities were maintained for more than 3 months. From the results presented herein, the polymerization system can be summarized as follows: In the early stage, MMA polymerization by TBBO proceeded following the mechanism proposed by Taira et al. Subsequently, all oxygen in the specimens was consumed, and TBBO functioned as a living radical polymerization initiator, as proposed by Muraki et al.

CONCLUSIONS

Based on the evaluation of the polymerization of MMA by the TBBO and BPO/amine systems, we can summarize the following conclusions.

1. We found distinct differences in the performance of MMA polymerization initiated by TBBO and by BPO/amine in terms of MMA conversion rate, molecular weight of the polymer, and the radical intensity during polymerization.

2. Polymerization by TBBO maintained its radical intensities for a longer period than that in the BPO/amine polymerization and it was maintained for more than 3 months.

3. The radical species produced in the TBBO-initiated PMMA after 72 h were still active enough as a polymerization initiator for MMA, while BPO/amine-initiated PMMA after 72 h has no activity in the initiation of the post-polymerization of MMA.

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