Preparation of Microcapsules Containing TMBA (1,3,5-trimethylbarbituric Acid) by the Drying-in-liquid Method and Its Application

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ABSTRACT: 1,3,5-trimethylbarbituric acid (TMBA), an amphiphilic material used widely for redox catalysts, such as organic peroxide, aromatic tertiary amine, and anhydride, was microencapsulated by the drying-in-liquid method with polyethylene methacrylate (PEMA) as a wall material. To prevent osmotically induced leakage of the core material into the continuous water phase during the microencapsulation process, TMBA was beforehand dissolved into the continuous water phase. In the experiment, the amount of TMBA dissolved and holdup of the dispersed oil phase were changed. The microencapsulation efficiency increased with the increase in the amount of TMBA dissolved but remained 36% at the highest even with the saturated level of TMBA. Also, the microencapsulation efficiency decreased with increase in holdup. The microcapsules containing TMBA were used for preparing a biological hard tissue-adhesive material and estimated for the microencapsulation effects. The adhesives containing the microencapsules were found to have excellent bonding properties and high storage stability. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 110: 2145–2152, 2008

Key words: microencapsulation; biomaterials; adhesives

INTRODUCTION

In recent years, bone fillers and bone cements used in the medical and dental fields have evolved remarkably. It is not an exaggeration to say that they are indeed the achievement of many studies carried out on biological hard tissue-adhesive monomers and radical polymerization catalysts (redox catalysts especially). In general, a polymerization initiator used commonly in the medical and dental fields is benzoyl peroxide (BPO), which is a heat-sensitive compound that rapidly breaks down to generate free radicals when heated. Also, BPO breaks down without heat. For instance, when it contacts with aromatic tertiary amine, it quickly breaks down even at room temperature to generate free radicals. These two ways for radical-generating mechanism of BPO have been applied for bone fillers and bone cements used in the medical and dental fields. The former mechanism requires heat. Namely, the half-life of BPO is 13 h at 70°C and decreases to 2.2 h at 85°C. When BPO breaks down, it generates benzoyloxy radical and a part of benzoyloxy radical further breaks down into phenyl radical. These free radicals have an activity capable of initiating polymerization. In the latter radical-generating mechanism, amine that is most typically used as a catalyst is *N*,*N*-dihydroxymethyl-*p*-toluidine (DMPT), which is usually dissolved in acrylic resin monomer. When the adhesive resin containing BPO contacts with monomer during mixing, it reacts with the monomer to generate benzoyloxy radical. More recently, *N*,*N*-dihydroxyethyl-*p*-toluidine (DEPT), which is more reactive and discolors the resin less than DMPT, have used instead of DMPT. On the other hand, to generate free radical for initiating polymerization, a reaction between 1,3,5-trimethylbarbituric acid (TMBA) and copper-ion or chloride-ion has been applied.[1–30] Thus, TMBA generates highly concentrated free radical and accelerates polymerization.[31–40]

The storage stability of TMBA, however, is extremely low due to its highly oxidizable nature as described earlier. Furthermore, when TMBA is used to prepare a biological hard tissue-adhesive material, TMBA with deliquescence easily agglomerates and induces aggregation between coexisting components such as polymer beads, leading to considerable difficulty in the handling operation. To avoid such

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TABLE I
Experimental Conditions for Microcapsule Synthesis

		Dispersed phase		Continuous phase	
No.	Hold up	TMBA (g)	Polymer soln.[a] (g)	TMBA (g) [wt %]	PVA soln.[b](g)
1	1.0	5.50	16.5	None [0]	300
2	1.0	5.50	16.5	5.6 [1.83]	↑
3	1.0	5.50	16.5	11.3 [3.63]	↑
4	1.0	5.50	16.5	22.5 [6.98]	↑
5	1.5	8.25	24.8	22.5 [6.98]	↑
6	2.0	11.0	33.0	22.5 [6.98]	↑

[a] Polyethyl methacrylate (D2528MELL, M_W = 80,000, Negami Chemical Industrial Co., Tokyo Japan) 30 wt %-MMA solution.
[b] Poly vinyl alcohol (n: 500, S.V. 86.5–89.0 mol % Nacalai tesque, INC, Kyoto, Japan) 4 wt % aqu. Solution.

problems, microencapsulation of TMBA has been anticipated. With these issues in mind, we tried to microencapsulate TMBA by the drying-in-liquid method in this study. It has been well known that the microencapsulation efficiency for hydrosoluble core materials in the microencapsulation method by use of (W/O)/W dispersion becomes extremely low because of leakage of core material to the outer water phase during the microencapsulation process.

In this study, to improve the microencapsulation efficiency, it is tried to repress this leakage by controlling the osmotic pressure and to investigate the physical effects of a biological hard tissue-adhesive material prepared using the microcapsules containing TMBA (TMBA-microcapsules).

EXPERIMENTAL

Materials

Materials used were polyethylene methacrylate (PEMA) (M_w = 80,000, Negami Chemical Industrial Co., Ltd., Ishikawa, Japan) as the microcapsule wall polymer, methylene methacrylate (MMA) (Mitsubishi Rayon Co., Ltd., Tokyo, Japan) as the low-boiling solvent for polymer, 1,3,5-TMBA (Nagase ChemteX Corp., Osaka, Japan) as the core material, and polyvinyl alcohol (PVA) (polymerization degree: 500, saponification value: 86.5–89.0 mol %, Nacalai Tesque, Inc., Kyoto, Japan) as a stabilizer.

Adhesive monomers of 4-acryloxyethltrimellitic acid (4-AET) and 4-acryloxyethyltrimellitic anhydride (4-AETA) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). BPO was purchased from Kawaguchi Chemical Co. Ltd. (Tokyo, Japan).

The components of powdery adhesive were PMMA (Mitsubishi Rayon Co., Ltd., Tokyo, Japan), PMMA-PEMA copolymer (Negami Chemical Industrial Co., Ltd., Ishikawa, Japan), and Si-treated silica fillers (1.5 μm in mean particle size), which were prepared by treating with γ-methacryloxypropyl trimethoxysilane (KBM-503, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan).

The components of liquid adhesive were 2-hydroxyethyl methacrylate (HEMA) (Mitsubishi Rayon Co., Ltd., Tokyo, Japan) and ethyleneglycol dimethacrylate (EGDMA) (shin-Nakamura Chemical Co., Ltd., Wakayama, Japan). Methoxy hydroquinone (MEHQ), butylated hydroxytoluene (BHT), *N*,*N*-dihydroxyethyl-*p*-toluidine (DEPT) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan) and used without further purification.

Preparation of TMBA microcapsules

The following is the method of preparing the TMBA-microcapsules. The experimental conditions are shown in Table I. More specifically, the given amount of MMA solution (30 wt %) dissolving PEMA was placed into a 150 mL PP beaker (55 mm in inside diameter, 70 mm in height), and TMBA of the specified amounts was added to the MMA solution. This solution was stirred for ~ 5 min using a PP spatula to prepare a primary dispersion. The continuous phase was ion-exchanged water (4.0 wt %) dissolving PVA and TMBA of the given amounts. Then, the continuous phase was transferred to a 500 mL flange-type separable flask with four stainless baffle plates (1.0 cm in diameter) and stirred at temperature of 40°C and the impeller speed of 200 rpm (40°C, 200 rpm) with a six-blade disk-turbine (5.5 cm in impeller diameter) until the temperature of the continuous phase became constant. The primary dispersion was then injected all at once into the continuous phase using a 50 mL disposable syringe. MMA of solvent was desolvated for 2–4 h at the impeller speed of 200 rpm and 40°C under reduced pressure of 700 mmHg and then, the TMBA-microcapsules were prepared. When MMA is removed, TMBA dissolved in MMA is precipitated and microencapsulated with PEMA. Vapor of MMA was trapped at

TABLE II
Composition of Experimental PMMA-type Adhesive Resin

Powdery adhesive (g)	PMMA	PMMA-PEMA	PEMA	SiO_2-powder	4-AET	4-AETA	BPO	TMBA
Adhesive-MC	40.0	45.0	15.0	15.0	2.3	0.8	0.3	MC[a] 2.05 (1.0)
Adhesive-BR	40.0	45.0	15.0	15.0	2.3	0.8	0.3	Bare 1.0
	MMA	HEMA	EGDMA		DEPT		MEHQ	BHT
Liquid adhesive	100.0	5.0	2.0		1.2		0.004	0.3

PMMA, poly(methyl methacrylate); PMMA-PEMA, copolymer of poly(methyl methacrylate) and poly(ethyl methacrylate); PEMA, poly(ethyl methacrylate); 4-AET, 4-acryloxyethyltrimellitic acid; 4-AETA, 4-acryloxyethyltrimellitic anhydride; SiO_2 powder (Si-treated silica): particle size 1.5 μm; BPO, benzoyl peroxide; TMBA, 1,3,5-trimethylbarbituric acid; MMA, methylmethacrylate; HEMA, 2-hydroxyethyl methacrylate; EGDMA, ethyleneglycol dimethacrylate; DEPT, *N,N*-dihydroxyethyl-*p*-toluidine; MEHQ, methoxy hydroquinone; BHT, butylated hydroxytoluene.

[a] Figures in parentheses indicate the amount of TMBA in microcapsule, wherein the content of TMBA in MC is 48.8%.

−100°C using EYELA UNITRAP UT-2000 (Tokyo Rikakikai Co, Ltd., Tokyo, Japan). The microcapsules prepared were filtrated under reduced pressure to be separated from the continuous phase. The separated microcapsules were thoroughly washed with ion-exchanged water, and freeze-dried for 3 days. After freeze-drying, the microencapsulation efficiency was calculated by the subtraction method. Namely, after the weight of microcapsules was measured, the microcapsules were dissolved by acetone. Then polymer was separated out and washed with water to remove TMBA. Then the weight of polymer (PEMA) was measured to estimate the mass of TMBA contained. The SEM observation of the microcapsules, followed by particle size measurement was also carried out.

Preparation of adhesive resins

Two kinds of PMMA-type adhesive resins (powdery and liquid type) were prepared by the compositions listed in Table II. The powdery adhesive (Adhesive-MC) was formulated using PMMA, PEMA, PMMA-PEMA, Si-treated fillers, adhesive monomers of 4-AET and 4-AETA, BPO, and TMBA-microcapsules. Control adhesive resin (Adhesive-BR) containing nonmicroencapsulated TMBA instead of the TMBA-microcapsules was formulated similarly. The liquid adhesive was formulated using MMA dissolving DEPT. The powdery adhesive resins were placed in 5, 23, and 40°C (75% relative humidity) in air for 2 months, respectively, and their bonding performance was then examined by mixing together with the liquid adhesive and the powdery adhesives. When two kinds of adhesives are mixed, the TMBA-microcapsules in the powdery adhesive are swollen with MMA in the liquid adhesive and then, TMBA is released. BPO in the powdery adhesive, contacts with DEPT in the liquid adhesive to generate free radicals. Also, BPO contacts with TMBA in the powdery adhesive to generate free radicals, when TMBA is not microencapsulated. It is necessary to add TMBA into the powdery adhesive in order not to discolor the resin.

Shear bond strength measurement

Preparation of adherents

Freshly extracted bovine incisors were used as substitutes for human specimens,[41] due to the large number of teeth required in this study. The bovine teeth, cut off the root, were embedded in epoxy resin, then ground into enamel or dentin using 600-grit SiC abrasive paper under running water, and then air-dried (ground enamel or dentin). A dental gold alloy (Shofu Super Gold Type 4, Shofu Inc., Kyoto, Japan) was cast with a casting machine (Shofu Argon Caster, Shofu Inc., Kyoto, Japan), and a gold alloy rod (6.0 ± 0.1 mm in diameter, 3.0 mm in height) was prepared. The gold alloy was embedded in an epoxy resin. Commercially pure titanium (CP Ti) was purchased from Daido Steel Co. Ltd. (Aichi, Japan). Adhesive surfaces of the SUS 303 rod (5.0 ± 0.1 mm in diameter, 6.0 ± 0.1 mm in height), the gold alloy and titanium (4.0 ± 0.1 mm in diameter, 6.0 ± 0.1 mm in height) were flat-ground using 600-grit SiC abrasive paper, and then sandblasted with aluminum oxide (40–50 μm) (Shofu Hi-alumina, Shofu Inc., Kyoto, Japan) under pressure of 5 kgf/cm^2. Then, the sandblasted SUS rod, gold alloy, and titanium metal were cleaned ultrasonically and dried at room temperature to prepare metal adherends (sandblasted SUS rod, gold alloy, and titanium metal).

Shear bond testing

The prepared adherends were treated with the surface-treating agents before adhesion. The adhesive surface of metal, i.e., the sandblasted SUS rod,

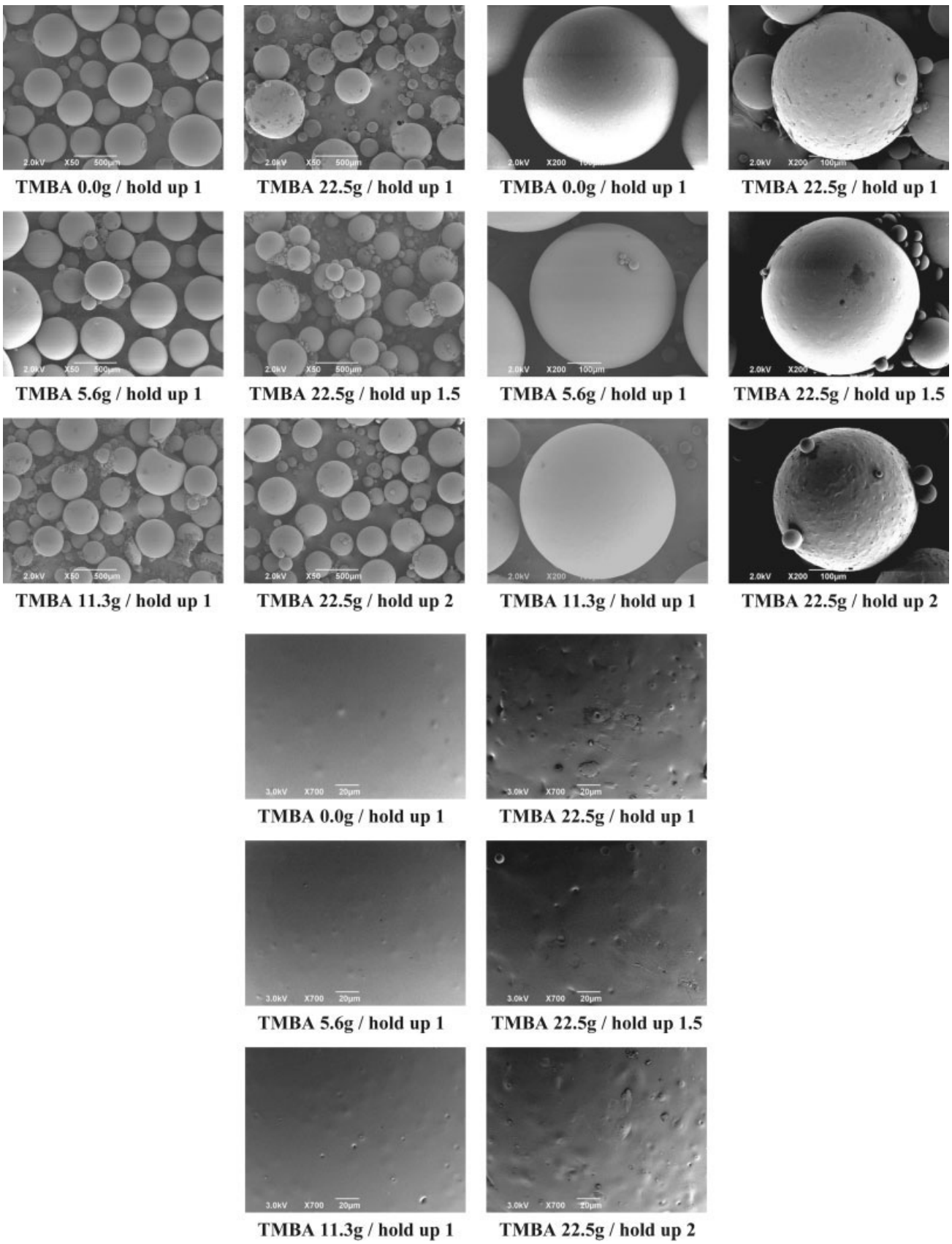


Figure 1 1-1, SEM photographs of microcapsules. 1-2, SEM photographs of microcapsules. 1-3, SEM photographs of surface of microcapsules.

titanium, and gold alloy, were treated with Metal-Link Primer (Shofu Inc., Kyoto, Japan) that is a metal primer for adhesion to precious and nonprecious metals. The SUS rod or gold alloy without Metal Link Primer treatment was also used as a control. The adhesive surface of ground enamel or ground dentin was treated with/or without ResiCem Primer (Shofu Inc, Kyoto, Japan) that is a self-etching primer for adhesion to enamel and dentin. Resin of the powdery adhesive and the liquid adhesive mixed by brush was placed on the adherends and made to bond between (1) the titanium and ground enamel or ground dentin treated with/or without surface-treating agents (YES: Metal-Link Primer for titanium, ResiCem Primer for ground enamel or ground dentin., NO: not treated with these primers) and (2) the SUS rod and the gold alloy. Load of 200 g was then applied on the titanium rod or SUS rod for the curing time. After 30 min, the test specimens ($n = 10$) were immersed in distilled water at 37°C for 24 h. The shear bond strength was measured using the mechanical testing machine (Instron-5543, Instron Co., MA) at the crosshead speed of 1 mm/min. All tests were conducted at 23 ± 1°C. Fractured surfaces of specimens were examined with the microscope, and adhesive failure, cohesive failure, and mixed failure were recorded. The mean and standard deviation for the load at failure were calculated and the results were subjected to a one-way analysis of variance (ANOVA), followed by the Newman-Keuls multiple comparison test.

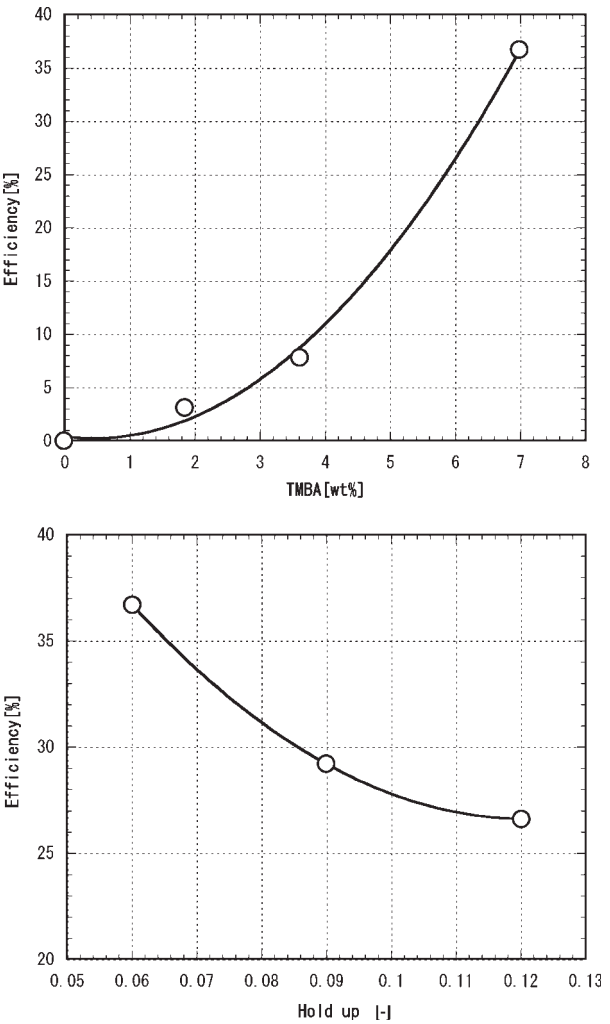


Figure 2 2-1, Dependence of microencapsulation efficiency on the TMBA concentration in continuous phase. 2-2, Dependence of microencapsulation efficiency on hold up.

RESULTS AND DISCUSSION

Morphological observation of TMBA microcapsules and measurement of diameter distributions

SEM images of the prepared microcapsules are shown in Figure 1-1, 1-2, and 1-3. It is observed that, although not visible in the lower-magnification photographs (50× and 200×), crater-like pores on the surface of the microcapsules increase more significantly as the TMBA concentration in the continuous phase increases. It may be pressured that the microencapsulation efficiency has to decrease with increase in number of pores. In this study, however, as is evident from Figure 2–1, the encapsulation efficiency increases with the TMBA concentration in the continuous phase. This may be thought to be due to the osmotic pressure adjusted by the addition of TMBA to the continuous phase. Accordingly, the pores on the surface of a microcapsule may not be the trace of core material leakage. This phenomenon may occur due to amphiphilicity of TMBA with hydrosolubility and hydrophobicity. More specifically, in order to mix MMA in the continuous phase and volatilized at the air/liquid interface, sufficient energy is required to go over the interface energy between the dispersed droplets of MMA and the continuous phase, but amphiphilicity of TMBA dissolving in the continuous phase may decrease the potential interface energy to activate evaporation of MMA. Thus, it may be considered that the pores resulted from evaporation of MMA, which was in a bumping state of a sort, being rapidly separated from the dispersion phase.

In the other hand, the saturated concentration of TMBA in the continuous phase dissolving PVA (4 wt %) is ~ 7 wt %. Because dissolution beyond the saturated concentration is chemically impossible, the microencapsulation efficiency of 35% under the addition of 7 wt % TMBA may imply that TMBA in the dispersed droplets was precipitated out due to contact with the continuous phase dissolving the saturated TMBA. Accordingly, the pores may be thought to be formed by both evaporation of MMA

and precipitation of TMBA. The relationship between hold-up and microencapsulation efficiency is plotted in Figure 2–2, which shows that the microencapsulation efficiency decreases with increase in holdup. It is generally considered that as holdup increases, it takes longer time for the dispersion of the dispersed phase to reach a dynamic equilibrium. Thus, longer the dispersion process of the dispersed phase, more the leakage of core material because of more break up of dispersed droplets. The dependency of the mean diameters of microcapsules on hold up and the TMBA concentration is shown in Figure 3–1 and 3–2, respectively. No effects of these factors were observed. The dependence of the microencapsulation efficiency on the mean diameter is shown in Figure 4. With the mean diameter, the microencapsulation efficiency decreases, becomes minimum, and then increases. The mean diameter is determined by dispersing behaviors of oil droplets such as coalescence and break up. As the microencapsulation efficiency is strongly affected by dispersing behavior described earlier, systematic discussion is impossible at present. It is necessary to investigate in detail the dependence of the microencapsulation efficiency on dispersing behaviors, namely the mean diameter.

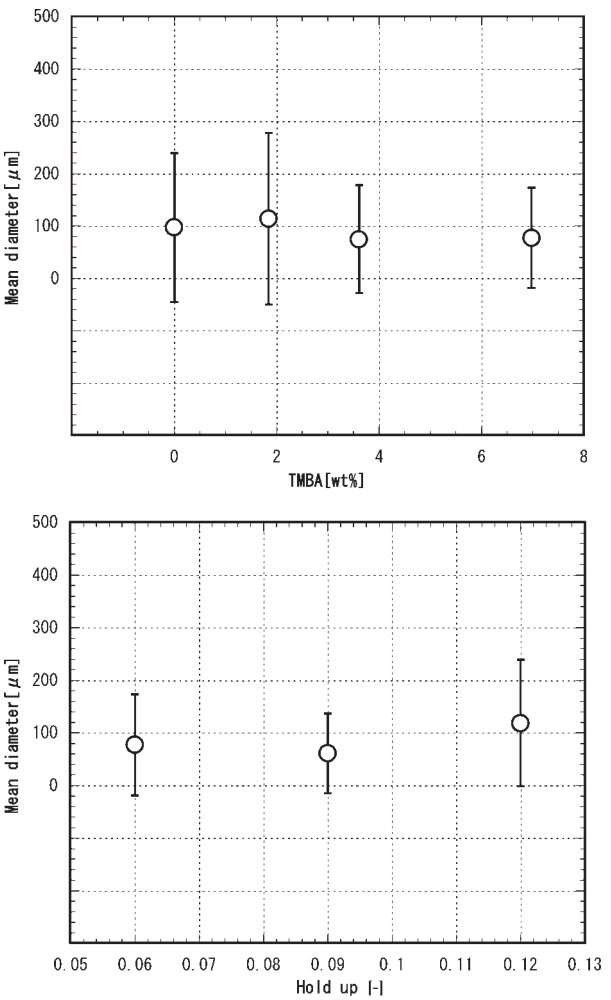


Figure 3 3-1, Dependence of mean diameters on the TMBA concentration. 3-2, Dependence of mean diameters on hold up.

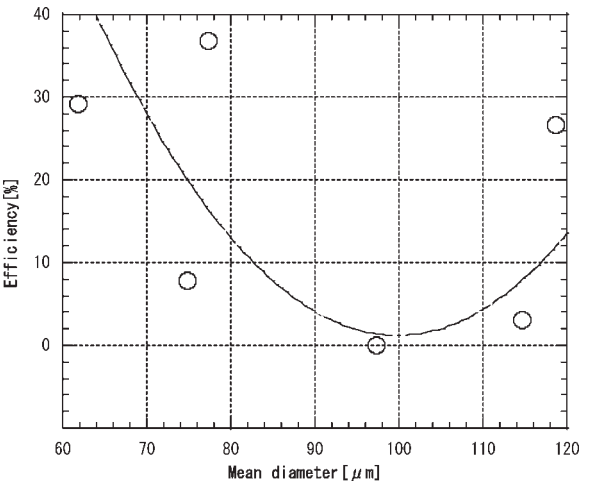
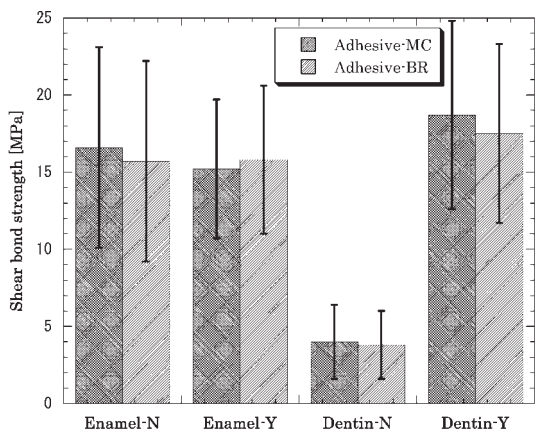


Figure 4 Correlation between mean diameters and the microencapsulation efficiency.

Shear bond strength measurement and activity of initiating polymerization

Figure 5 presents the results of the shear bond strength between the sandblasted titanium and unetched ground enamel or unetched ground dentin with/or without surface-treating agent. The statistical analysis (ANOVA) indicated that there were no significant differences between Adhesive-MC and Adhesive-BR for the bond strengths to unetched



Enamel-Y, Dentin-Y: Treated with Metal-Link Primer for titanium and ResiCem Primer for ground enamel or ground dentin.
Enamel-N, Dentin-N: Not treated with primers for surfaces of all specimens.

Figure 5 Shear bond strength of experimental adhesive resin between titanium and unetched ground enamel or unetched ground dentin.

ground enamel (15.2–16.6 MPa) treated with/or without surface-treating agents ($P < 0.05$). Although there was no significant difference between Adhesive-MC and Adhesive-BR for the bond strengths to unetched ground dentin treated with surface-treating agents and to unetched ground dentin without surface-treating agents ($P < 0.05$), there were significant differences between the bond strength to unetched ground dentin treated with surface-treating agent (17.5–18.7 MPa) and that without surface-treating agent (3.8–4.0 MPa) ($P < 0.05$). Figure 6 represents the shear bond strengths of Adhesive-MC and Adhesive-BR between the sandblasted SUS rod and sandblasted gold alloy treated with Metal-Link Primer after the storage periods of starting (Initial), 1 month (1 *M* at 5, 23, and 40°C), 2 months(2 *M* at 5, 23, and 40°C) in a relative humidity of 75%, respectively. The statistical analysis indicates that the bond strengths of Adhesive-MC to gold alloy maintained [starting: 42.5 (3.7) MPa] after 2-month storage period at 5°C [41.8 (4.8) MPa] and 23°C [39.5 (8.1) MPa], 1-month storage period at 40°C [31.0 (9.8) MPa], and 100% mixed failure (M) of adhesive resin were observed on the fractured surfaces, respectively, ($P < 0.05$). To the contrary, the bond strength of Adhesive-BR to gold alloy after 2-month storage period at 23°C [12.8 (6.4) MPa] was significantly decreased with 90% adhesive failure (A) ($P < 0.05$), and the bond strength using the Adhesive-BR stored for 1-month and 2-month period at 40°C could not be tested. Although there were no significant difference between Adhesive-MC and Adhesive-BR in the bond strengths after 2-month storage period at 5°C and 1-month storage 23°C, there were significant difference between both adhesive resins for the bond strengths after 2-month storage period at 23°C and 40°C ($P < 0.05$). Powdery property of Adhesive-MC was not significantly changed during 2-month storage period with good mobile handling property, such as brush on technique. In the contrast, Adhesive-BR was markedly changed during 1-month storage at 40°C caused by agglomeration of the powdery adhesive (Fig. 7), which was adverse handling property, especially brush on technique of PMMA-type adhesive resin.

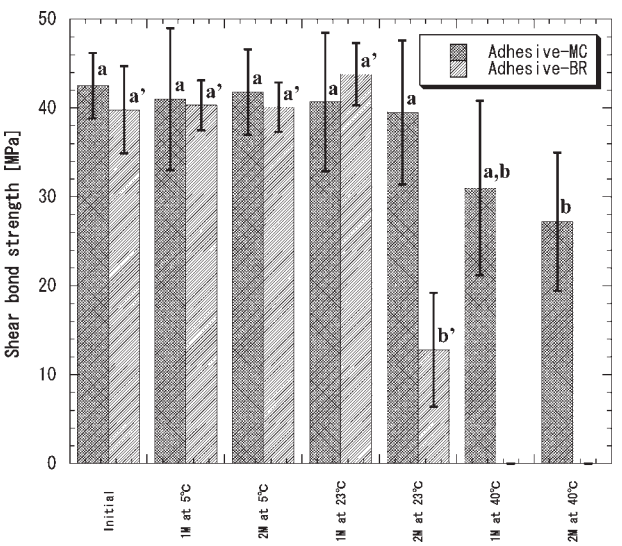


Figure 6 Shear bond strength of experimental adhesive resin between SUS rod and gold alloy.

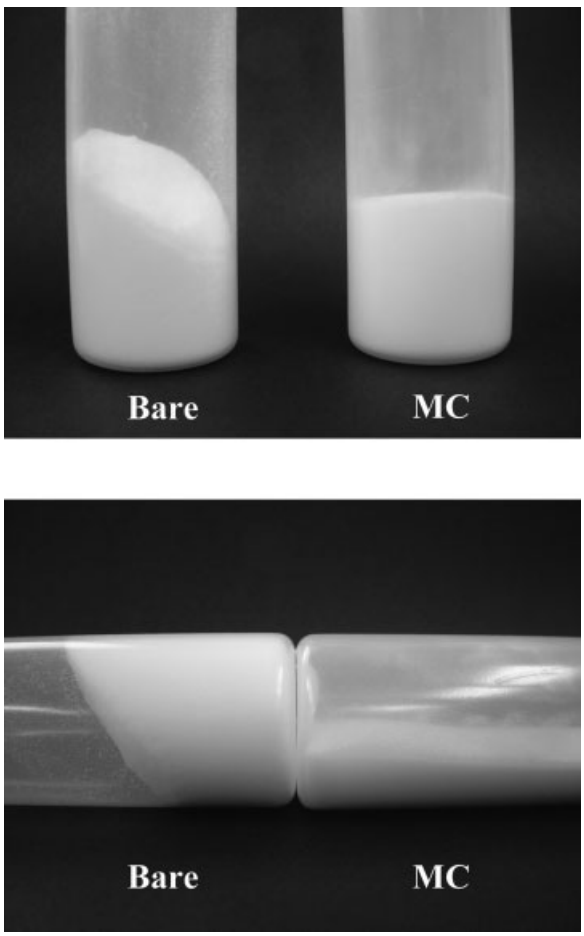


Figure 7 A photo of the powdery adhesive of bare BPO/Amine initiator after 1-month storage at 40°C (75% relative humidity).

CONCLUSIONS

In this study, TMBA was microencapsulated with PEMA by the drying-in-liquid method. We evaluated the surface morphology, the particle diameter distributions, and the microencapsulation efficiency together with their possibility for use in adhesive biomaterials. The results obtained are as follows.

1. Microcapsules containing TMBA were able to be prepared by using PEMA as shell material, PVA as an organic surfactant, and MMA monomer as volatile solvent.

2. The maximum microencapsulation efficiency of TMBA was around 0.36 under the experimental conditions adopted here.
3. Higher hold up of dispersed phase resulted in the lower microencapsulation efficiencies.
4. Microcapsules had the ability for initiating polymerization after 2-month storage at 40°C and relative humidity of 70%

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