Stability of Benzoyl Peroxide in Methyl Alcohol

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The purpose of this study was to clarify the stability of benzoyl peroxide (BPO) in some solvents. BPO was dissolved in acetone, acetonitrile (AcCN), 50% acetonitrile-50% distilled water (50% AcCN), ethyl alcohol (EtOH), and methyl alcohol (MeOH). Solutions containing BPO were incubated for eight days at 25°C. In MeOH, BPO rapidly decomposed into benzoic acid (BA) and methyl benzoate (MeBA) time-dependently, whereas BPO in acetone, AcCN, and 50% AcCN was relatively stable. Although BPO in EtOH was slightly stable within the first 24 hours, it decomposed time-dependently such that BA and EtBA as decomposition products of BPO were produced. These results indicated that the stability of BPO in a solution was dependent on the solvent and the decomposition rate of BPO dissolved in MeOH was the fastest. These suggest that BPO can decompose even in lower-than-activation temperature by the solvent to use for its dissolution.

Key words : Benzoyl peroxide, Stability, HPLC

INTRODUCTION

Benzoyl peroxide (BPO) is commonly used as a polymerization initiator in the dental field and in polymer production, flour bleaching, and acne medications3). In the dental field, BPO is well known to be contained in autopolymerizing resins such as the base polymer and composite resin.

As BPO is a highly reactive chemical, benzoic acid (BA) is formed by the decomposition of BPO in some solvents such as diethyl ether and diethyl cellosolve at low temperatures (<37°C)2). In addition, BPO is decomposed in various solvents such as ethers, alcohols, phenols, and amines at 79.8°C3-5). However, the kinetics of BPO decomposition has been just a matter of reporting in these reports and the decomposition products of BPO are not described in detail2-3). It is well known that the degradation of BPO in solutions progresses via a free radical mechanism2-5). In the first step at high temperatures, BPO decomposes and produces benzoate radicals. It is considered that these benzoate radicals accelerate the reaction by reacting with BPO or the solvent to propagate the chain reaction.

Although the stability of BPO in medications depends partly on the solvents used3), limited data exist regarding the effect of solvents on the stability of BPO at room temperature. However, for cured resins used in dentistry, it is very important to measure accurately the level of residual BPO and that of BPO leached.

The purpose of this study, therefore, was to elucidate the stability of BPO in some solvents and the decomposition products of BPO using high-performance liquid chromatography (HPLC).

MATERIALS AND METHODS

BPO Standard for thermal analysis (purity: >99%) was used as BPO in this study, and was purchased from Wako Pure Chemical (Tokyo, Japan). Acetone, acetonitrile (AcCN), ethyl alcohol (EtOH), and methyl alcohol (MeOH), which were solvents of HPLC grade, were likewise purchased from Wako Pure Chemical (Tokyo, Japan). In addition, BA and methyl benzoate (MeBA) were purchased from Wako Pure Chemical (Tokyo, Japan), and ethyl benzoate (EtBA) from Tokyo Kasei (Tokyo, Japan). BA, MeBA, and EtBA were of analytical grade, and their purity was approximately more than 98%.

BPO was dissolved in acetone, AcCN, 50% (v/v) AcCN-50% (v/v) distilled water (50% AcCN), EtOH, and MeOH, where the final concentration was approximately 3μg/ml. The reason why BPO of such a low concentration was chosen was because of our aim to precisely determine the level of BPO remaining in the cured resins. These solvents containing BPO were incubated for eight days at 25°C. An aliquot of these solvents was taken every 24 hours for eight days and prepared as a sample for HPLC.

The HPLC system was an Agilent 1100 with diode array detection (Agilent Technologies Deutsch-
land GmbH, Waldbronn, Germany). HPLC conditions are shown in Table 1. A reversed phased C18, Capcell Pak C18 MGII (250 mm × 2 mm i.d.; Shiseido, Tokyo, Japan) with a guard cartridge, Capcell C18 MG II (10 mm × 2 mm i.d.; Shiseido, Tokyo, Japan), was used. The mobile phase was AcCN and 10 mM NaH$_2$PO$_4$ adjusted to a pH of 3.5 with phosphoric acid. Gradients were set as follows. Time from 0 to 4 min: 40% AcCN; time from 4 to 30 min: linear gradient of AcCN from 40% to 90%; time from 30 to 40 min: 90% AcCN; time from 40 to 45 min: linear gradient of AcCN from 90% to 40%; time from 45 to 60 min: 40% AcCN. Injection volume was 20 µl, and the UV wavelength used for detection was 238 nm. Peaks for BA, BPO, EtBA, and MeBA were identified primarily by retention time with respect to the calibration standards, and diode array spectral match and peak purity (ChemStation software, Rev.A.10.01J, Agilent Technologies) were used to confirm identity. Each stock solution of BPO, BA, MeBA, and EtBA was prepared in AcCN with a concentration of 3 µg/ml and stored at -25°C. Then, six standard solutions of the mixture of BPO, BA, MeBA, and EtBA from 0.1 to 5 µg/ml in AcCN were made by successive dilutions in AcCN. Standard curve was represented by the plots of the peak area. Amount of a component was quantified based on the standard curve.

### RESULTS

Presently, various HPLC methods are used to detect BPO and BA. In this study, however, the mixture of BPO, BA, EtBA, and MeBA was determined simultaneously using gradient analysis. The instrument detection limits under gradient conditions were 18.8 ng/ml for BPO, 21.1 ng/ml for BA, 22.8 ng/ml for EtBA, and 22.9 ng/ml for MeBA. As for the instrument quantification limits, they were 62.8 ng/ml for BPO, 70.3 ng/ml for BA, 75.9 ng/ml for EtBA, and 76.4 ng/ml for MeBA.

To examine the stability of BPO in solvents, BPO was dissolved in acetone, AcCN, 50% AcCN, EtOH, and MeOH at a concentration of approximately 3 µg/ml at 25°C. For BPO in acetone, AcCN, and 50% AcCN, it was stable for eight days at 25°C (Fig. 1). In EtOH, BPO was relatively stable for the first 24 hours of incubation at 25°C (Figs. 1 and 2). After the first day, BPO decomposed into BA and EtBA time-dependently where the amounts of BA and EtBA increased with the decomposition of BPO, as shown in Fig. 2. BA, EtBA, and BPO were identified having a retention time of 8.3, 24.2, and 30.4 minutes, respectively. EtBA was identified from UV spectra using spectral match and peak purity (the insertion chart of Fig. 3). As shown in Fig. 4, the amounts of BA and MeBA increased with the decrease of BPO. By the degradation of BPO, the stoichiometric molar ratio between BA and MeBA was 0.9:1. Within the duration examined, there were no changes in the amount of BA dissolved in MeOH and EtOH (data not shown).
In the present study, the stability of BPO in a solution was dependent on the solvent used. When BPO was dissolved in acetone, AcCN, and 50% (v/v) AcCN at 25°C, it was not degraded. However, BPO in EtOH and MeOH decomposed into BA and benzoates. In addition, a simple and reliable HPLC method for quantifying BPO and benzoates simultaneously was developed.

Generally, when measuring an individual substance using HPLC, an isocratic analysis is higher sensitivity than a gradient one. The former cannot measure individual substances at the same time but the latter one can. As unstable substances such as BPO are considered to be liable to be changed time-dependently under a certain condition, it cannot be determined accurately using the isocratic analysis but rather by the gradient analysis. Indeed, the mixture...
of BPO, BA, EtBA, and MeBA could be determined simultaneously using our gradient analysis. This method thus showed itself to be easy to use and highly precise for the simultaneous determination of BPO and its degradation products.

It has been known that various factors contribute to the stability of BPO in solutions: solvent, BPO concentration, and temperature. Studies have shown that BPO (197mM) decomposes promptly in solvents such as acetone, EtOH, and MeOH under vacuum at 79.8°C. After one and two hours in acetone, percent decompositions of BPO are 28.5% and 43.0%, respectively. However, in this study, BPO in acetone at 25°C did not decompose and was relatively stable even after eight days (Fig. 1). This difference in result might well reflect that of experimental conditions, such as an oxygen-free condition and the concentration of BPO. Oxygen and hydroquinone are known to be inhibitors to radical chain reaction. Accordingly then, because our experimental conditions were not oxygen-free, BPO in acetone might be stable. In addition, as the concentration of BPO used in this study was lower than that of previous reports, it could be hard for the radical chain reaction to occur. However, if the radical chain reaction cannot occur because BPO concentration in solution is low, there remains the further question why BPO degraded in MeOH and EtOH. Hence, the problem cannot be resolved by merely focusing on the concentration of BPO used. More detailed examination will be needed to clarify this discrepancy.

BPO in EtOH decomposes by about 82% within 10 minutes at 79.8°C under an oxygen-free condition. In the present study, BPO in EtOH was slightly decomposed within one day at 25°C. After eight days at 25°C, only 40% of BPO was decomposed (Fig. 2). When in MeOH, the percentage decomposition of BPO is 33% within three minutes and 46% within five minutes. Therefore, the decomposition rate of BPO in MeOH at 79.8°C is slower than that in EtOH. In the present study, the percentage decomposition of BPO in MeOH was approximately 60% after one day and approximately 40% after eight days in EtOH (Fig. 1). Our results hence suggest that the decomposition rate of BPO in MeOH is faster than that in EtOH at 25°C. Apparently, between the previous report and our present study, there was a vast contrast in the degradation rate of BPO in MeOH and EtOH. In the previous report, the degradation rate of BPO in EtOH at 79.8°C is faster than that in MeOH, whereas our present results were contrary. These differences in the decomposition rate of BPO could be attributed to the experimental conditions described above, although the causes of these differences are still unclear.

Benzoic acid (BA) is known to be a degradation product of BPO, but there are little reports on the other degradation products of BPO except for BA. In the present study, it was shown that BPO in MeOH decomposed into BA and MeBA. Stoichiometrically, one molar equivalent of BPO should be decomposed into two molar equivalents of BA. However, the molar ratio between BA and MeBA was 9.1 (Fig. 4), suggesting that the generation rate of MeBA was slightly faster than that of BA. Thus, the degradation of BPO in MeOH could not be regarded as a simple radical reaction.

Generally, alcohols and ethers facilitate the decomposition of BPO due to the chain transfer mechanism. As one possibility to explain the generation of MeBA by BPO in MeOH, by the benzoate radicals attacking the solvent, new radicals which are more stable or less reactive than the benzoate radicals are generated in MeOH if the chain transfer to the solvent will occur. In addition, there was not much of the possibility that BA was converted into MeBA in MeOH (or into EtBA in EtOH) by the esterification reaction, because no changes in the amount of BA in MeOH or EtOH were detected within the duration examined.

There is a strong possibility of underestimating the level of residual BPO in a cured resin if alcohols were used as the extractant for extracting components remaining in the cured resin. Furthermore, if MeOH will be used as the extractant, MeBA may be detected. As for MeBA, interpretation of whether to be added to the ingredients as an additive becomes difficult. In this way, interpretation of obtained results may be difficult whether MeBA is added as an additive when supplied from the manufacturer or whether it is generated by a chemical reaction. To avoid these confusions, it is advisable that alcohols should not be used as the extractant for the extraction of components remaining in the cured resin used in dentistry.

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