치의학박사 학위논문

The Effect of N-acetylcysteine Addition on the Polymerization Behavior of PMMA Bone Cement

N-acetylcysteine 첨가가 PMMA 골 시멘트의 중합에 주는 영향

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-ABSTRACT-

The effect of N-Acetylcysteine Addition on the Polymerization Behavior of PMMA Bone Cement

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Wearing dental acrylic prosthesis may cause adverse reactions to oral tissues due to bioactive leaches from resins such as residual methyl methacrylate (MMA). N-Acetylcysteine (NAC), a well-known thiol-containing antioxidant, may alleviate the toxicity of polymethyl methacrylate (PMMA) bone cement through the inactivation of the monomer components in the cement by its sulfhydryl moiety. This study aimed to reveal the effects of NAC on the polymerization heat, degree of conversion (DC), mechanical properties, and residual monomer release of PMMA bone cement by adding 0.25, 0.50, 0.75, and 1.00 wt. % NAC to PMMA powder. Measurements were performed 5 times per experimental groups and averaged. The data were analyzed with One-way ANOVA and Tukey test with $p<0.05$ as significance level.

1. The peak temperature of PMMA cements during polymerization (T_{max}) was significantly reduced and setting time (t_{set}) was steadily delayed with the increasing NAC percentage.

2. The DC of all experimental PMMA bone cements reached as high as 91% after 7 days of incubation, as determined by Fourier-transform infrared spectroscopy (FTIR).
3. The experimental groups showed steady declines in flexural strength and surface hardness as a fraction of increasing NAC. Meanwhile, the mechanical properties of the experimental groups were improved with time.
4. The amount of MMA leached into deionized water was analyzed using high performance liquid chromatography (HPLC). It was found to increase with immersion time up to 24 hours, after which no significant change was observed.
5. Results showed a linear correlation between thermal characteristics, mechanical properties and the released MMA amount with the DC of the experimental groups. The potential usefulness of NAC in developing more biocompatible PMMA bone cement for increased working performance was highlighted in this study.

Keywords: PMMA bone cement, N-acetylcysteine, polymerization behavior, degree of conversion, monomer release

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CONTENTS

I. Introduction

Acrylic resins have been applied widely in dentistry for denture bases, artificial teeth, resin cements, and orthodontic appliances (Consani et al.; Rantala et al., 2003; Schmid-Schwap et al., 2009). Commonly used acrylic resins are prepared by mixing polymethyl methacrylate (PMMA) powder with methyl methacrylate (MMA) liquid. The solid phase is composed of spherical polymer PMMA copolymer powder containing an initiator (dibenzoyl peroxide, BPO) and a radiopacifier (ZrO_2 or $BaSO_4$). The main ingredient of the liquid part is MMA monomer, which contains the activator N, N-dimethyl-*p*-toludine (DMPT) (Kuehn et al., 2005).

Two things should be taken into consideration before the clinical application of PMMA bone cements: the polymerization heat and residual monomer release. *In vitro* study, the polymerization of acrylic resin is an exothermic reaction through which 544 J/g heat is produced and causes the local temperature to rise to a peak value ranging from 80℃ to 124℃ (Saha and Pal, 1984). Due to the thin cement coating, which should not exceed 5 mm, and the temperature dissipation *via* the large prosthesis surface and the local blood supply, Eriksson and Alberksson (Eriksson and Albrektsson, 1984) determined the temperature threshold for impaired bone regeneration to be in the range of 44-47℃ for 1 minute of exposure *in vivo*, which is much lower than *in vitro* application. Elevated temperature in the bone may lead to thermal necrosis and tissue damage, ultimately resulting in failure of the prosthetic fixation (Dunne and Orr, 2002).

Ideally, during polymerization of acrylic resin, all monomer molecules would be converted to polymers. The degree of conversion (DC) also plays an important

role in determining the physical properties of the polymeric material such as shrinkage, strength, surface hardness, *etc.* (Wu et al., 2010). High DC is associated with improved mechanical and chemical properties, color stability, and biocompatibility (Urban et al., 2007). However, the conversion of MMA monomers to polymers is incomplete, and some unreacted monomers remain after polymerization (Bartoloni et al., 2000; Urban et al., 2009).

The DC of acrylic resin is affected by many factors such as environmental temperature, curing time, filler content, and monomer ratio (Amirouche-Korichi et al., 2009; Wu et al.). Several quantitative analyses of residual MMA in acrylic resin have been introduced, such as high performance liquid chromatography (HPLC) (Kawahara et al., 2004), gas chromatography (GC) (Sadamori et al., 1990), Fourier-transform infra-red spectroscopy (FTIR) (Rueggeberg, 1994) and "wet" chemical analysis (Smith and Bains, 1956). All of these techniques have their own particular advantages. Due to their specificity and sensitivity, FTIR and HPLC have been the most common methods for determining the features of dental polymers (Duray et al., 1997). FTIR detects the two bands arising from stretching vibrations of the carbonyl group (C=O) at 1725 cm^{-1} and the vinyl group (C=C) at 1640 cm^{-1}, directly before and after polymerization of the materials (Urban et al., 2009).

The MMA monomer is cytotoxic, and the potential toxic effects of unreacted MMA on patients have caused much concern (Giunta and Zablotsky, 1976; Gonçalves et al., 2006; Kedjarune et al., 1999). Several studies have shown that acrylic resins release the highest amount of residual MMA monomer during the first 24 hours after initial polymerization, followed by a longer-lasting moderate

leaching (Çelebi et al., 2008; Kedjarune et al., 1999; Nunes et al., 2003). Reports have demonstrated that polymerization radicals could decrease the amount of residual monomer *via* further polymerization over time, which could also improve the physical properties after polymerization (Harrison et al., 1977). To determine the amount of released monomer, HPLC is highly recommended (Çelebi et al., 2008).

N-acetylcysteine (NAC) is a well-known cysteine derivative, which works as an antioxidant agent for maintain the balance of anti-oxidant redox system and plays a key role in direct scavenging of free radicals (Gillissen and Nowak, 1998). Recently, researchers have demonstrated that NAC-supplemented acrylic resins restore the suppressed viabilities and functions of dental pulp cells, oral fibroblasts, or osteoblasts to a biologically significant degree (Aita et al.; Kojima et al., 2008). Previous studies have evaluated the setting and mechanical properties of PMMA bone cement supplemented with NAC buffer (Tsukimura et al., 2009). It was demonstrated that the addition of NAC into bone cement did not affect the temperature during polymerization but did reduce the setting time. The flexural strength and compressive strength were not altered. However, the relationships between the DC and thermal characters, mechanical properties, and elution of residual monomers of different fractions of NAC-supplemented PMMA over time have not been fully investigated.

This study was performed to evaluate the effects of NAC addition to PMMA on the thermal and mechanical properties of PMMA bone cement over a 7 days elution time. In addition, the effect of NAC-incorporated PMMA bone cements on released monomer was analyzed for a 28 days period. Moreover, the

correlations among DC and thermal and mechanical properties and the amount of monomer released from experimental PMMA bone cements were also investigated.

II. Literature Review

1. Acrylic Bone Cement

The search for alternative dental materials which can assist the surface as a mode of treatment for dental repairing has been an issue over years. As the patients demand better aesthetic, function and comfortable dentures, a great process began towards improvement in the quality of materials used for fabricating dentures. Polymethyl methacrylate (PMMA) was developed 70 years ago, since Rohm and Hass introduced PMMA in sheet form and Nemours in powder form. Acrylic based resins are frequently used in daily dental practice, as they are able to provide the essential properties and necessary characteristics to be used in diverse functions. Most common use of the materials includes denture bases and liners, provisional restorations, orthodontic appliances and temporary crowns (Dubois et al., 1999; Hamza et al., 2004; Kojima et al., 2008; Mutluay and Ruyter, 2005).

Acrylic based resins consist of polymeric materials based on PMMA. These dental materials are the result of a free radical polymerization reaction (Kuehn et al., 2005). Acrylic resin is the most widely used materials for construction of dentures which can be classified as autopolymerized polymers, heat-polymerized polymers, light-activated and microwave-cured materials. For heat-polymerized materials, heat can be generated by hot water bath while the light polymerizing uses visible light as energy source. Microwave can activate the polymerization of microwave-cured materials.

In spite of its disadvantages of dimensional changes during polymerization, porosity and allergic/cytotoxic effects, Dr. Walter Wright introduced PMMA as a denture base materials and it is still frequently used for fabrication of denture bases

due to its esthetic characteristics, low modulus of elasticity and reduced cytotoxic properties, high processing and polishing abilities, relining and rebasing possibility and low cost (Tandon et al., 2010). Here, we present the chemical composition, polymerization process, released monomer and biological side effects in the applying of autopolymerized acrylic based resins bone cement.

1.1 Composition of Autopolymerized Acrylic Based Resins

Most denture bases materials are supplied with polymer powder in primary packaging and monomer liquid in an ampule as a so called "two system". The major component of powder is beards of pre-polymerized PMMA or polyethyl methacrylate (PEMA) powder with diameter up to 100 μm. These are produced by a process of suspension polymerization in which MMA monomer, containing peroxide initiator (BPO) which remaining unreacted after the production of the beads, in addition to extra peroxide added to the beads after their manufacture. The powder also contains a radiopacifier, either zirconium dioxide (ZrO_2) or barium sulfate ($BaSO_4$), required for cement visibility in radiographs.

The major ingredient of liquid is MMA monomer, which accounts for 97-99 wt. % (Leggat and Kedjarune, 2003). It is a clear colorless, low-viscosity liquid with a boiling point of 100.3℃ and an intensely smelling by a relatively high vapour pressure at room temperature. MMA is an ester of methacrylic acid with a polymerizable double bond. Cross-linking agents such as ethyleneglycoldimethacry -late (EDGMA), trimethylolpropane trimethacrylate (TMPTMA) or 1, 6-hexanediol

dimethacrylate (HDDMA) are suggested to added to improve or retain the resin mechanical properties (Deb and Vazquez, 2001). N, N-dimethyl-*p*-toludine (DMPT)

(0.4 -2.8 wt%), a tertiary amine that acts as an activator is incorporated into the liquid in order to react with the BPO in the powder to create free radicals with the initiate, accelerate the polymerization reaction, eliminating the need to preheat the material prior to polymerization (Tihan et al., 2009). To prolong the shelf life of MMA, an inhibitor, such as amounts of hydroquinone (15-75 ppm) is also added to MMA to prevent spontaneous polymerization during storage of the product (Fujisawa and Kadoma, 1992).

Denture lining materials are classified as hard reline materials, tissue conditions and soft lining materials. The materials which used to provide a chairside reline to the denture are hard reline materials. Tissue conditions are soft denture liners which may be applied to the fitting surface of a denture. Denture soft lining materials are very similar to the tissue conditions but are not as soft as the issue conditions immediately after setting but retain their soft for longer, taking up to a month or two to harden. Though denture lining materials are of several types and are used for a variety of reasons, there composition are generally supplied as a PMMA or PEMA powder and liquid which mixed together (Mutluay and Ruyter, 2005). The liquid is made of monomer components, such as methyl, ethyl or butylmethacrylate and a mixture of plasticizer phthalate, or pigment such as isobutylmethacrylate. The soft denture lining materials provide a temporary cushion which prevents masticatory loads from being transferred to the underlying hard and soft tissues (Gupta, 2010). Soft lining materials are very similar to tissue conditions, which supplied with PMMA powder and a mixture butylphthalyl butylglyconate plasticizer and ethyl alcohol solvent.

Orthodontic appliance is a device which is used to adjust the shape or alignment of

teeth. Removable appliances have a long history in orthodontic treatment. They are used for space maintenance, thumb deterrent, tipping teeth, overbite reduction, block movements, and retention. PMMA is the most commonly used material for manufacturing the polymeric part of removable orthodontic appliances (Faltermeier et al., 2007).

1.2 Polymerization Process of Autopolymerized Acrylic Based Resins

When constructing an autopolymerizing material, the two-component system powder and liquid components are mixed together (Silikas et al., 2005). Mixing is followed by a gradual increase in viscosity is due to a combination of physical and chemical changes occurring in the mix. Smaller acrylic beads are dissolved in the monomer and become "swollen". In addition, the polymerization of monomer is initiated when peroxide from the powder and chemical activator from the liquid meeting during mixing. Thus, conversation of monomer to polymer contributes to the increase in viscosity. Generally, these materials reach the "dough" stage quite quickly and remain workable for a short period of time. Within a few minutes of attaining a dough consistency, the mobility of remaining monomer molecules is hindered at high conversion rates and the material becomes hard and unmanageable. The rate of polymerization increase rapidly causing a large temperature rise. The conversion of monomer to its polymer may not be complete and residual monomer is left over in the polymeric matrix (Koroglu et al., 2012). Over the few weeks to months after curing, the amount of monomer remaining unpolymerized decreases.

As the polymerization proceeds, double C=C (π-bonds) are converted to new C–C (α-bonds). The C–C bond has energy about 350 kJ/mol, and the C–C π-bond has 270

kJ/mol. The difference in energy between the two bonds, 80 kJ/mol, emits as heat (Altintas et al., 2008). Since the polymerization of acrylic bone cement is exothermic, with the maximum polymerization temperature being high enough that inflammation of pulp, irreversible pulpitis, or pulp necrosis in severe cases may occur (Zach and Cohen, 1965).

1.3 Released Monomer from Autopolymerized Acrylic Based Resins

Radical polymerization of the MMA in bone cement generally does not proceed to completion, because the mobility of remaining monomer molecules is hindered at high conversion rates. There is, therefore, varying amounts of free or unreacted monomer remain in the polymerized. The main part of the total residual monomer is post-polymerized slowly, a smaller part of the residual monomer is released and metabolized to carbon dioxide in the water in the citric acid in cycle (Koroglu et al., 2012).

The released monomers from different types of acrylic based resins have been widely studied (Bural et al., 2011; Lamb et al., 1982). Most of the investigations are taken on denture relining materials of different chemical composition (Giampaolo et al., 2011; Santos Nunes Reis et al., 2006; Urban et al., 2006). Fewer studies analyze orthodontic appliances (Kopperud et al., 2011) and temporary crowns (Dubois et al., 1999). Until now, no standard has been set for testing of release acrylic bone cement residual, generally the experimental conditions consists in incubating polymer specimens of different shapes, such as disks, rectangular or cylinders, and sizes prepared according to manufactures instructions in a liquid, at room temperature or 37◦C, for periods of time ranging from few hours to several months. Sadamori et al.

(Sadamori et al., 1992) conducted a continuous longer study from 1 to 17 years on the release of residual monomer on maxillary denture base resins.

For the immersion of acrylic resin cement, most of the researches use water as the leaching solution (Giampaolo et al., 2011; Kopperud et al., 2011; Koroglu et al., 2012; Lamb et al., 1982; Wady et al., 2011). In order to increase the solubility of water insoluble compounds, ethanol and mixtures of ethanol/water has also been used in order to increase the solubility of water insoluble compounds like phthalates (Boeckler et al., 2008; Urban et al., 2006). Pfeiffer and Rosenbauer (2004) and Urban et al. (2006) have also taken acetone for as the leaching media for better solubility of compounds released from acrylic bone cement.

Researchers also use unstimulated whole human saliva and artificial saliva for residual monomers and other leachable components diffusion from acrylic bone cement. Kedjarune et al. (1999) used unstimulated whole human saliva to investigate the release of MMA from heat-cured and autopolymerized denture base materials. Urban et al. (2009;, 2011) evaluated leaching compounds of hard chairside reline resins in artificial saliva. For the diffusion of phthalates and other esters of aromatic carboxylic acids, PBS aqueous buffer and urea were added as components in saliva.

Very few clinical investigators have conducted study on the release of compounds from acrylic based materials in human month. Gonçalves et al. (2008) evaluated, in situ, the effect of two manipulation and two polishing techniques on the residual monomer of an autopolymerized acrylic resin on 40 volunteers for 24 hours. Concentrations of residual monomer were significantly reduced after 24 hours after polymerization.

Results showed that residual monomers are eluted within the first hours after initial

polymerization and the release is a time-dependent effect. In Buyukerkmen and Ozturk's study (Buyukerkmen and Ozturk, 2010), polymerized resins release the highest amount of uncured monomers during the first 24 hours after being cured, followed by a slow and moderate release over a long period of time to 30 days. In a long-term research period, Sadamori et al. (Sadamori et al., 1992) claimed that MMA decrease could be expressed in a hyperbola. Amount of released monomer was reported to decrease in the first 5 years; however, residual monomer still could be detected in dentures which used up to 17 years.

In order to avoid the adverse effects and decrease the amount of uncured monomer, several researchers have suggested that immersion dentures in water before placing them on the patient (Ozdemir et al., 2009; Urban et al., 2009; Urban et al., 2011). Reducing the amount of residual monomers after the treatment depends on the diffusion of these monomers in the water also in accordance with the immersion time. Urban et al.'s (2011) study showed that residual monomers of denture base materials can be reduced by hot water bath after the polymerisation treatment.

1.4 Biological Effects of Monomer Release

Since PMMA is the most widely used resins in acrylic based resins in dentistry for fabricating of dentures and orthodontic appliances, the release of MMA monomers of the polymerization system from dental composites has been considered as problem of a wide variety of adverse biological reactions, including local and systemic toxicity and pulp reactions, leading to irreversible disturbance of basic cellular functions (Kojima et al., 2008; Minamikawa et al., 2010). Various *in vitro* and *in vivo* experiments and cell based studies conducted on acrylic based resins or their residual

monomers.

Cell culture techniques have provided strong evidence that released compounds from acrylic based resins may induce a series of biological responses on cells. In spite of different experiment methodologies, the majority of researches focused on the cytotoxicity elution of unbound components mainly MMA monomer and its derivatives (Bural et al., 2011; Hautamäki et al., 2010; Kedjarune et al., 1999; Vojdani et al., 2010). Both permanent (L 929 fibroblast and osteoblast) and primary cells as gingival fibroblast, dental pulp, periodontal ligament and epithelial cells are used in the studies (Bural et al., 2011; Hautamäki et al., 2010; Kojima et al., 2008; Lai et al., 2004; Sipahi et al., 2006). Though Test systems vary considerably in the way cytotoxicity is measured, at the cellular level, all indicate changes in basic cell structures, such as cell membrane integrity and cell functions like enzyme activities or the synthesis of macromolecules (Att et al., 2009) .

Although still not clear, the mechanisms of adverse effects caused by MMA monomer are thought to involve direct toxicity from released or residual MMA and oxidative stress created by free radicals that are released during the resin polymerization (Att et al., 2009; Huang and Chang, 2005). In the past few years, molecular biological methods have provided new insight on cellular response to residual monomer. Ishikawa et al. (2006) investigated the pleiotropic effects of MMA by systematically identifying the genes differentially expressed after exposure of the mouse fibroblast cell line L929. Hattori, et al. (2008) showed that MMA increased glutathione S-transferases alpha 1 gene promoter activity through anti-oxidant responsive element-mediated promoter activation. Cell culture techniques have also provided strong evidence that residual MMA monomer in acrylic based resin

biomaterials may cause genotoxicity (Iz et al., 2010). Lai et al. (2004) investigated MMA cytotoxic effects on primary gingival fibroblasts and periodontal cells of varied concentration, which showed that the residual monomer affected the viability of both primary gingival fibroblasts and periodontal cells in a dose-dependent manner.

2. An Antioxidant : N-acetylcysteine

N-acetylcysteine (NAC) is a sulfhydryl-containing compound which composed of L-cysteine and acetyl (Moist et al., 2010). NAC is shown to be the precursor in the formation of cysteine and glutathione in the cells with a significant antioxiant effect. In humans it can be administered orally or by intravenous infusion and can also be inhaled using a nebuliser. NAC has been used as a mucolytic ("Mucus dissolving") agent to help break up the thick mucus often present in people suffering from chronic respiratory ailments over 30 years (Sadowska, 2012). Now widely available in supplement form, NAC is currently being recommended to have a significant effect in treating hepatotoxicity, preventing and treating conditions of oxidative stress and reduced GSH levels caused by diseases such as HIV/AIDS and cancer, and alleviate toxicity from chemo- and radiotherapy (Atkuri et al., 2007). Here, we discuss the mechanism action of NAC as an antioxidant and anti-inflammatory.

2.1 An Antioxidant and Glutathione Precursor

Glutathione is a small protein produced in the body from cysteine, glycine, and glutamic acid. It is the body's most powerful antioxidant and free radical scavenger. N-acetylcysteine (NAC) helps the body produce more glutathione as a therapeutic

antioxidant stems from its role as a precursor of cysteine. Under conditions of oxidative stress, the cellular production of reactive oxygen species (ROS) exceeds the cell's antioxidant capacity, glutathione becomes depleted, cellular macromolecules such as lipids, proteins and DNA can be damaged (Yamada et al., 2008). This can be reversed by NAC supplementation which reduces hydroperoxides by glutathione peroxidases and conjugation reactions that are catalyzed by glutathione-S-transferases (Dickinson and Forman, 2002). Therefore, glutathione is therefore essential for the body's antioxidant defenses.

D'Antò et al.'s (2011) study showed that incubation of human gingival fibroblasts (HGF) with NAC significantly reduced ROS production and decreased the cell damage and cytotoxicity caused by all composite orthodontic primer.

2.2 An Anti-inflammatory

NAC also works as an anti-inflammatory by inhibiting the production of pro-inflammatory transcription factors activator, known as tumor necrosis factor alpha (TNF-α) (Peristeris et al., 1992). Fujisawa et al. (1996) investigated the treatment of synovial cells with NAC, it showed that NAC has inhibited TNF-α-induced nuclear factor kappa beta (NF-κB) activation and transcription. Moreover, NAC also inhibited synovial cell proliferation induced by TNF alpha. It has been reported that these transcription factor is mediated by ROS in regulating the progression of the inflammatory process, leading to the hypothesis that the anti-inflammatory properties of NAC are due to its mechanism of action as an antioxidant.

In Sato et al.'s (2009) study, NAC showed a dose-dependent manner of reducing

proliferation, transcriptional expression, and collagen production in oral mucosal cells without cytotoxic effects. Furthermore, NAC substantially reduced the hydrogen peroxide (H_2O_2)-induced inflammatory elevation of cellular proliferation and collagen production.

3. Objective

The goals of our thesis are to (1) determine the changes of thermal properties, mechanical properties and degree of conversion after addition of amount of NAC to the PMMA acrylic bone cement; (2) study the residue monomer amount of NAC-supplemented PMMA after polymerization with time elution.

Ⅲ. Materials and Methods

1. Materials

Pre-polymerized PMMA powder with an average molecular weight of 800,000 Da (average particle size of 25 μm) and MMA liquid were obtained from Fluka (Yongin, Korea). Zirconium oxide (ZrO_2) and NAC were from Aldrich (St. Louis, USA), benzoyl peroxide (BPO) was purchased from Sigma (Steinheim, Germany). N, N-dimethyl-p-toludine (DMPT) was purchased from Aldrich (Milwaukee, USA). All products were used as received without further purification. The powder was prepared using a pestle to thoroughly mix the pre-polymerized PMMA (84.0 wt.%), radiopacifier ZrO_2 (15.0 wt.%), and BPO initiator (1.0 wt.%) in a ceramic mortar. The combination was then rotated in a ball mill machine (YoungHan, Korea) for 4 hours to obtain a homogeneous mixture. The liquid monomer was prepared by mixing MMA (98.0 wt.%) and the DMPT accelerator (2.0 wt.%) in a screw-top brown glass bottle which was then sealed tightly. To provide a uniform source of solid dispersed aqueous solution, a certain amount of NAC was dissolved in deionized water at room temperature. Different amounts of pre-polymerized PMMA powder were added to the NAC solution to obtain NAC in total fractions of 0, 0.25, 0.50, 0.75, and 1.00 wt.%. After the PMMA powders and NAC solution were mixed thoroughly, the PMMA suspensions were stored in a dry oven at 38 ℃ for 48 hours to obtain dry PMMA-NAC powders. The experimental NAC-supplemented PMMA bone cements were prepared by mixing the liquid (MMA) and powder (PMMA) containing various concentrations of NAC. All of the specimens were tested at a powder-to-liquid mass ratio of 2:1 at ambient temperature.

2. Thermal Properties

The peak temperature during polymerization (T_{max}) and setting time (t_{set}) of PMMA cements were estimated in compliance with International Standard Organization (ISO) Specification No. 5833:2002. The solid mixture NAC-supplemented PMMA powder was placed in a rubber bowl. The liquid monomer (MMA) was slowly added in a weight fraction of 50% with respect to the solid PMMA while mixing by hand at room temperature for 60 seconds. The polymerization reaction induced a visually observable change in the mixture's viscosity. After mixing, the dough was transferred to a mold which is 10mm diameter and 6mm thick. The detection needle of the thermometer (TECPEL 318 Thermometer) was inserted into the center of the dough-like mixture to continuously record the temperature as the reaction progressed. For mixing and test condition, the room temperature was 23±1℃ and the relative humidity (RH) was no less than 40%. Peak temperature (T_{max}) represented the maximum temperature achieved during the polymerization process. Setting time (t_{set}) of the PMMA bone cement was defined as the time at which the temperature increase was halfway between the maximum temperature and the ambient temperature (Endogan et al., 2009). For all experimental PMMA bone cement groups, the test specimens were prepared by mixing 20 g powder with 10 g liquid monomer. Means and standard deviations of peak temperature and setting time (n=5) were calculated and analyzed using ANOVA and Tukey multiple comparison tests at a significance level of 0.05.

3. Degree of Conversion (DC)

The DCs of all the experimental PMMA bone cements from 5 minutes to 7 days after polymerization were analyzed using FTIR spectroscopy (Perkin-Elmer spectrophotometer, USA). The absorbance peaks of the cured and uncured cements were obtained using 20 scans in the range of 2000-1500 cm^{-1} at a resolution of 4 cm^{-1}. The samples were analyzed as films with potassium bromide windows. Five specimens were used to determine the ratio of each experimental group. A blank KBr crystal was used for the collection of the background spectrum. The DC of each specimen was estimated based on the ratio of absorbance intensities of the C=C peak height from the methacrylate group at 1640 cm^{-1} to that of the unchanging C=O peak from the ester group at 1725 cm^{-1} as follows:

$$DC\% = \left(1 - \frac{(Abs(c=c)/(Abs(c=o)\text{polymerized specimen})}{(Abs(c=c)/(Abs(c=o)\text{monomer})}\right) \times 100$$

Using the ratio between the two absorbances, the fraction of unreacted double bonds could be calculated. MMA liquid with no DMPT mixed with each percentage of uncured NAC-PMMA powder was used as the controls.

4. Flexural Strength and Surface Hardness

Flexural strength was tested in compliance with ISO 4049:2009. Five specimens were prepared in a rectangular-shaped teflon mold (length 25±0.2mm, width 2±0.1mm, thickness 2±0.1mm) and were incubated at 23±1℃ at time intervals of

2 hours, 24 hours, and 7 days. After incubation, a three-point bending test was performed with a universal testing machine (Instron 4465, USA) at a cross-head speed of 1 mm/min to determine the point at which fracture occurred. Means and standard deviations of flexural strength (n=5) were calculated and analyzed using ANOVA and Tukey multiple comparison tests at a significance level of 0.05.

After flexural strength testing, five fragments from each experimental group were used for surface hardness testing. A Vickers diamond indenter attached to a microhardness indenter machine (HMV-2, SHIMADZU, Japan) was used for all of the specimens at a 490.3 mN load for 10 seconds. The values were converted to VHN numbers. Three indentations were made on each specimen. Means and standard deviations of surface hardness (n=15) were calculated and analyzed using ANOVA and Tukey multiple comparison tests at a significance level of 0.05.

5. Released Monomer Content

Disk-type (12×2.0 mm) specimens were allowed to polymerize for specific times (20 and 40 minutes) and were then immersed in 2 mL HPLC grade water in a sealed container. Specimens were stored separately at room temperature for various time intervals of 100 minutes, 24 hours, 7 days, 14 days, and 28 days of immersion.

For the quantification of the residual MMA, 20 μL aliquots of extraction solution were injected into the HPLC (Waters Instruments, USA) and separated in a reverse-phase C18 column (Inertsil ODS-4, length: 250 mm, internal diameter: 4 mm, particle size: 5 μm, Japan). The mobile phase was 67%

methanol with 33% water in isocratic conditions at a flow rate of 1.0 mL/min. Detection was performed at UV 205 nm. The concentration of released monomer was determined by comparing the peak areas with that of known amounts of MMA solution *via* calibration graphs. Samples which polymerized for 40 minutes before immersion were used as controls. All liquids used were of HPLC grade (Merck, Germany). The following equation was used to calculate the weight percentage of the residual monomer MMA in the sample solutions:

$$\text{Residual monomer (wt. \%)} = \frac{C_{monomer}(mg/mL) \times 2mL \times 100}{\text{Mass of specimen (mg)}}$$

6. Statistical Analysis

Mean and standard deviation were estimated for each group. Mean values were compared between different study groups using One-way ANOVA with $p<0.05$ as significance level and student' *t-test*. Tukey multiple comparison tests was employed to identify the significant groups at 5% level.

Ⅳ. Results

1. Thermal Properties

The time evolution of measured temperature during the polymerization process of the experimental PMMA bone cements is shown in Figure 1. All of the curves exhibited a bell shape. The setting time of polymerization was defined as the time at which the temperature increase was halfway between the maximum temperature and the ambient temperature. The setting characteristics of the analyzed experimental bone cements are summarized in Table I.

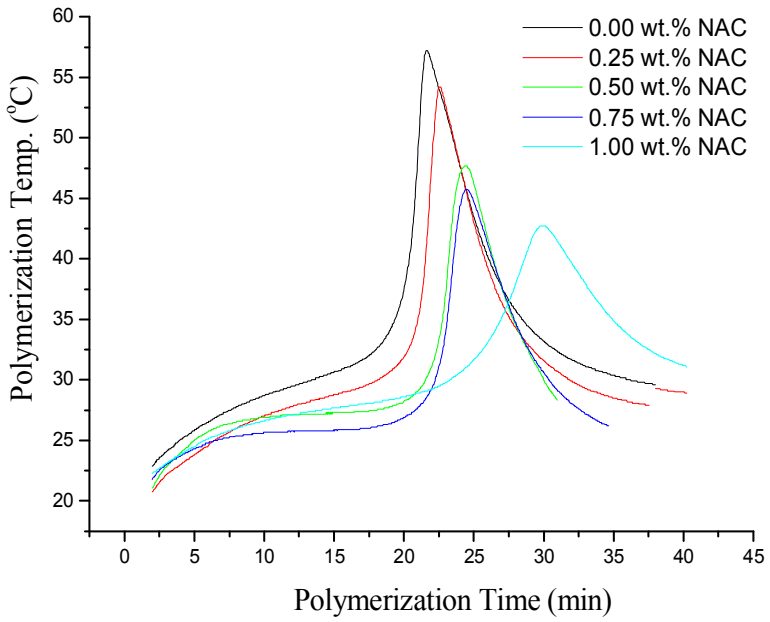


Figure 1. Polymerization temperature versus time for experimental PMMA bone cements with various NAC fractions.

TABLE Ⅰ

Thermal properties of PMMA with NAC.

Bone Cement NAC (wt. %)	Thermal properties	
	T_{max} (°C)	$t_{setting}$ (min)
0	56.98±0.49[a]	20.75±1.22[f]
0.25	53.86±0.42[b]	23.28±0.96[g]
0.50	47.16±0.95[c]	25.76±0.76[h]
0.75	45.84±0.65[d]	25.42±0.71[h]
1.00	42.58±0.55[e]	28.89±1.02[i]

Note: the same superscript letters within the same column are not significantly different (p>0.05).

Adding NAC to PMMA bone cement led to a significant reduction in exothermic polymerization. The maximum temperature (T_{max}) was reduced from 57.0±0.5 to 42.6±0.6 ℃, while the NAC fraction increased from 0 to 1 wt.%. The polymerization setting time was 20.8±1.2 minutes without NAC, increasing to 28.9±1.0 minutes with 1 wt. % NAC.

2. Degree of Conversion

Figure 2 presents FTIR spectra of polymerization of two different experimental PMMA bone cements during a period ranging from 5 minutes to 7 days in the region of 1900-1550 cm^{-1}. It was obvious that the intensity of C=C absorbance at 1640 cm^{-1} was getting weaker as time elapsed. Comparing Figure 2a with Figure 2b, it can be seen that the weakened C=C absorbance of specimens without NAC was greater than that of specimens with 1 wt.% NAC.

Figure 3 shows the DCs for experimental PMMA bone cements as a function of time (up to 7 days). During the first 120 minutes, the DCs of PMMA bone cements with 0 and 0.25 wt.% NAC increased significantly to more than 90%, whereas PMMA bone cements with NAC concentrations ranging from 0.5 to 1.00 wt.% experienced a lower DC during the first two hours, up to 75%. After one day, the DC of every sample increased steadily. 7 days later, the DCs of five experimental groups were greater than 91%. In particular, the DCs of PMMA bone cements with 0 and 0.25 wt.% NAC were 97.4±1.5% and 98.0±1.5 %, respectively.

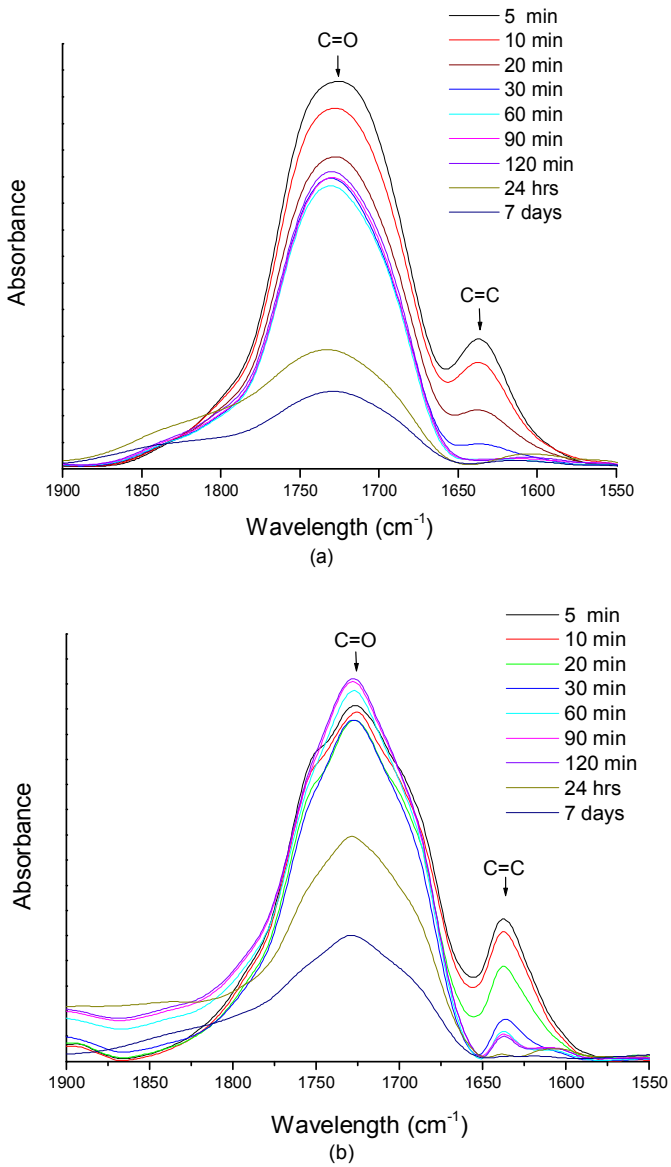


Figure 2. FTIR spectra of polymerization of experimental PMMA bone cements without NAC (a) and with 1.00 wt.% NAC (b) 5 minutes to 7 days after mixing.

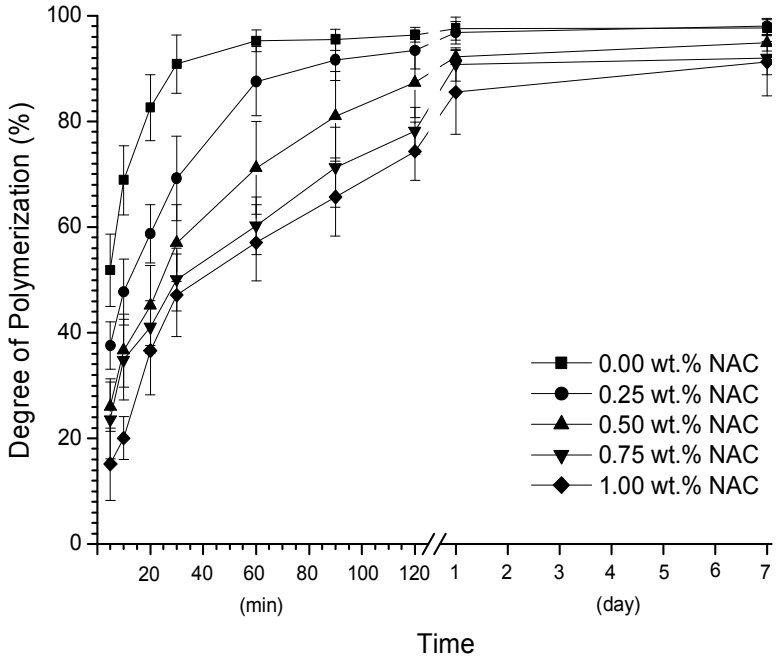


Figure 3. Degree of conversion of experimental PMMA bone cements at specific time after mixing.

3. Mechanical Properties

The three-point bending test and surface hardness results of all experimental groups after every incubation time are presented in Table II. There was an obvious increase in flexural strength for each of the NAC-supplemented PMMA bone cements as time elapsed. The PMMA with 0.25 wt.% NAC exhibited a flexural strength of 70.4±1.2 MPa, which was comparable to that of 0 wt.% (74.0±3.4 MPa) after 7 days. The PMMA with 1.00 wt.% showed the lowest flexural strength of 47.8±1.2 MPa at 7 days.

TABLE II

Flexural strength and Microhardness of Experimental Bone Cements

NAC in PMMA (wt. %)	Flexural strength (MPa)			Microhardness (VHN)		
	2 hours	24 hours	7 days	2 hours	24 hours	7 days
0.00	59.80±0.79[a]	68.49±0.61[e]	73.98±3.41[j]	15.56±0.70[a]	16.76±0.97[d]	17.87±0.84[g]
0.25	47.76±1.02[b]	58.84±0.84[f]	70.39±1.17[k]	13.22±0.62[b]	14.49±0.38[e]	16.93±0.56[h]
0.50	43.73±1.59[c]	56.12±0.68[g]	65.21±1.53[l]	13.45±0.68[b]	14.30±0.65[e]	16.39±0.38[i]
0.75	41.05±4.50[c,d]	51.68±1.80[h]	55.10±3.35[m]	13.11±0.66[b]	14.59±0.65[e]	16.21±0.56[i]
1.00	37.78±4.18[d]	42.88±3.17[i]	47.80±1.18[n]	11.76±0.56[c]	13.38±0.85[f]	14.88±0.53[j]

Note: the same superscript letters within the same column are not significantly different (p>0.05).

The trend of surface hardness was similar to the three-point bending measurement. The microhardness values of PMMA bone cements without NAC steadily increased from 15.6±0.7 to 17.9±0.8 VHN in 7 days, while PMMA containing NAC from 0.25 to 0.75 wt.% all hardened to 16 VHN.

4. Released Monomer Content

Residual MMA released into water was quantified using HPLC during five time intervals, and the results are shown in Figure 4. The chromatography of MMA monomers from NAC-supplemented PMMA at 1 and 0.25 wt% of 100 minutes immersion after PMMA polymerization for 20 minutes for an example by HPLC analysis was shown in Figure 4 (a). It showed that the MMA peak came out at 6.2 minute.

Data showed that MMA leaching from bone cement began simultaneous when immersed in deionized water. The lowest residual MMA monomers obtained from PMMA polymerized for 20 minutes were got from 100 minutes after immersion (Figure 4b) (from 0.20±0.03 wt.% to 0.52±0.03 wt.% as NAC increased from 0 to 1 wt.%). Figure 4 also showed that the quantities of released MMA greatly increased in the first 24 hours, followed by longer-lasting moderate leaching. The residual monomers leached out of the cement for 7 days, but showed little subsequent change afterwards (0.28±0.003 wt.% to 0.78±0.001 wt.% as NAC increased from 0 to 1 wt.% over 28 days of immersion). More than 80% of the leachable MMA was eluted from each experimental bone cement within 24 hours. In the control group (Figure 4b), samples polymerized for 40 minutes before immersion released much less MMA during the 28 day storage

period than samples polymerized for 20 minutes before immersion (from 0.13±0.06 wt.% to 0.39±0.27 wt.% as NAC increased from 0 to 1 wt.% over 28 days of immersion).

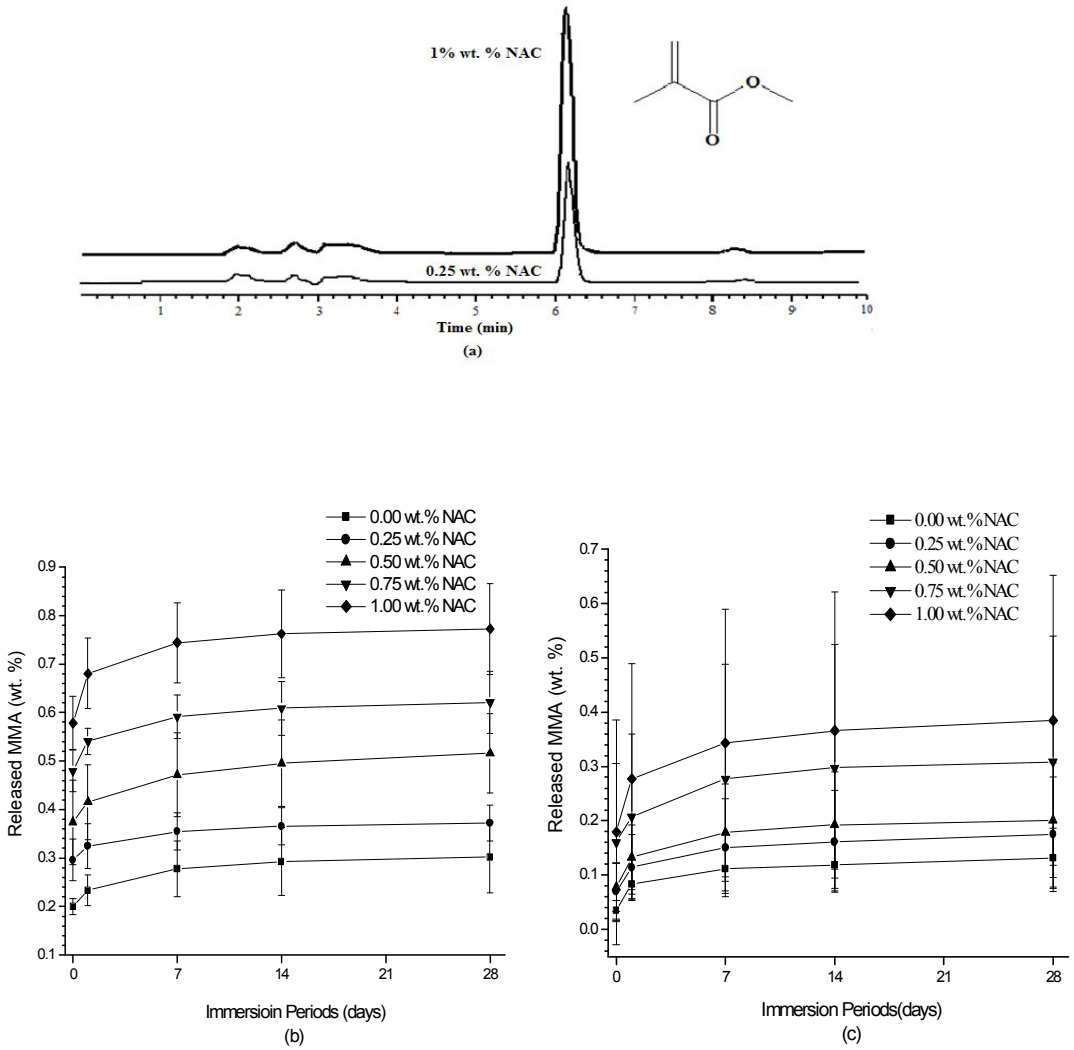


Figure. 4 HPLC analysis of MMA from NAC-supplemented PMMA at 1 and 0.25 wt% of 100 minutes immersion after PMMA polymerization for 20 minutes for an example (a). Weight percentage of released MMA with time elution of 100 minutes, 24 hours, 7, 14, and 28 days immersion after which PMMA polymerized for 20 minutes (b) and 40 minutes (c), respectively.

Ⅴ. Discussion

Due to its many advantages, PMMA bone cement is commonly used in daily clinical practice and has already experienced much success as a clinically essential material. However, research has indicated that the exothermic heat during bone cement polymerization could lead to necrosis in the tissues surrounding the prosthesis. Moreover, leachable substances from acrylic-based resins, such as MMA monomer, could cause allergic reactions (Kiec, 1996). In an *in vitro* study, incorporation of the thiol-containing antioxidant NAC into acrylic resin cement protected the dental pulp cells against resin-induced death (Kojima et al., 2008). Two mechanisms are related to the adverse effects of the resin monomer at the cellular level. One is the genetic damage caused by the electron-withdrawing ability of methacrylates, which can destroy cellular components, such as DNA and protein (Geurtsen and Leyhausen, 2001). The other is the oxidative stress occurring from depletion of intracellular glutathione to produce reactive oxygen species (ROS) (Schweikl et al., 2006). Study of resin monomer evoked late apoptosis which accompanied by a marked increased in intracellular ROS indicated the oxidative stress was thought to be the principle cytotoxic reason of bone cement monomer (Yamada and Ogawa, 2009).

N-acetylcysteine (NAC) is a well-known thiol-containing antioxidant cysteine derivative which could easily deacetylated into cysteine. As cysteine is an important precursor of glutathione, it could significantly inhibit the cytotoxicity caused by increased ROS levels that activate pathways leading to apoptosis (Aita et al., 2010). NAC can also alleviate the toxicity of as an oxidant scavenger through the inactivation of PMMA bone cement monomer by its sulfhydryl

moiety (Gillissen et al., 1997). Unfortunately, the time-associated effects and degree of conversion on thermal characteristics, mechanical properties, and the amount of leachable monomer in NAC-supplemented PMMA bone cements have not been systematically studied.

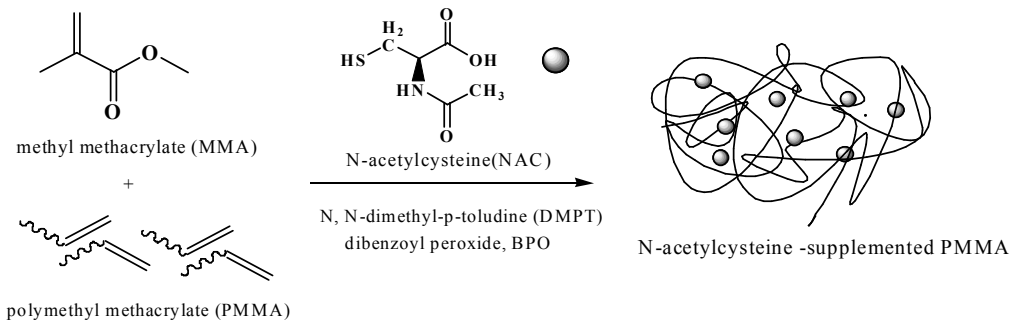
It has been suggested that the relative amount of NAC-incorporation in bone cement leads to no adverse effects on the thermal and mechanical properties of PMMA bone cements (Tsukimura et al., 2009). In the present research, the effects of increasing fractions of NAC on the thermal behavior, mechanical properties, and the amount of released uncured monomer over time of the cements were further investigated. Moreover, we also evaluated the correlations between DC with thermal properties, mechanical properties over 7 days and released monomer over 28 days of PMMA bone cement.

The polymerization process of PMMA bone cement is a complex process, with the PMMA powder taking up the monomer liquid during simultaneous chemical and physical reactions. The swelling and dissolution processes are important to assure the proper working characteristic of the cement, while the carbon-carbon double bond of monomer polymerization is responsible for the final hardening of the PMMA bone cement.

The DC of PMMA bone cement is an important property because both the mechanical properties and monomer elusions are related to the percentage of free radical monomer-to-polymer conversion within resin-based materials (Ferracane and Greener, 1986; Tuusa et al., 2005). Our study confirmed that the polymerization of PMMA bone cement was a time-associated reaction and demonstrated that most of the monomers were produced within the first two

hours after polymerization, followed by a slow and moderate conversion in the following days, as shown in Figure 3. The influences of DC on the mechanical properties of PMMA bone cement could be further illustrated in this paper.

The results of this study demonstrated that, even in very small amounts, the addition of NAC into experimental PMMA bone cement decreased the polymerization temperature. All of the NAC-PMMA bone cements exhibited a decreased maximum polymerization temperature, with values ranging from 53.9 to 42.6 ℃. The decreased polymerization heat could be attributed to the presence of solid material NAC particles that is homogeneously distributed in the PMMA cement dough which reduced the DC involved in the exothermic reaction of polymerization, causing a decreasing of the environment temperature respect to MMA monomer (Deb and Vazquez, 2001).

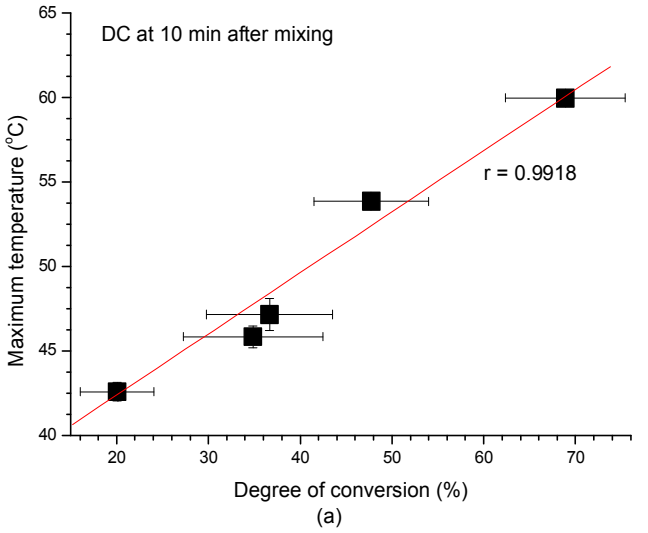


Scheme 1. Polymerization of N-acetylcysteine -supplemented PMMA

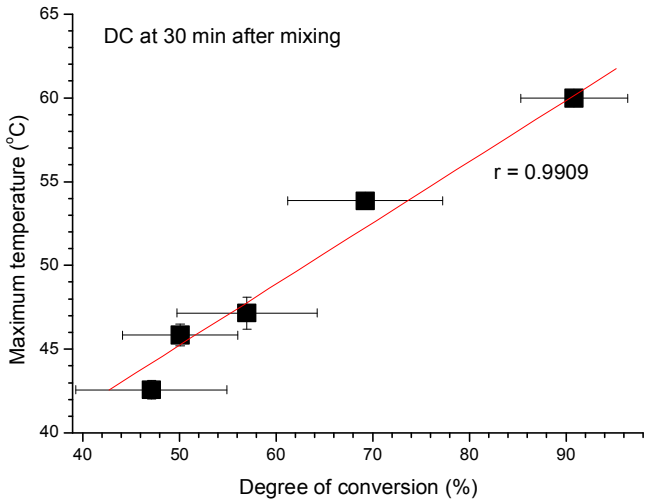
It is known that commercially available PMMA bone cements exhibit substantially exothermic temperatures as high as 124 ℃ *in vitro* (Saha and Pal, 1984), which often causes the death of surrounding tissues (Dunne and Orr, 2002). Based on this undesirable side effect, the lower exothermic temperature of the NAC-cooperated PMMA is beneficial for use in clinical practice. The process of polymerization of NAC -supplemented PMMA is shown in Scheme 1.

The correlation between DC and maximum polymerization temperature at 10 and 30 minutes after mixing are shown in Figure 5. The maximum temperature increased as DC increased in cements with different amounts of NAC, showing a good correlation (r=0.9918 at 10 minutes, r=0.9909 at 30 minutes). This confirmed the release of heat during carbon-carbon double bond polymerization. The more the carbon-carbon double bond polymerized, the higher was the maximum polymerization temperature.

The observation that a greater amount of NAC decreased the polymerization peak temperature of the bone cement does not mean that as much NAC as possible should be added before bone cement polymerization. The delayed setting time of bone cement arises from the slower polymerization reaction and will extend the time that bone tissues are exposed to unreacted monomer, thus increasing the risk of tissue necrosis (Madrala and Nuño, 2010; Vallo, 2002). Adding NAC to PMMA bone cement will delay the polymerization setting time, which may not be beneficial to the self-curing process.



(a)



(b)

Figure 5. Correlation between degree of conversion and maximum temperatures of experimental PMMA bone cements: (a) 10 minutes and (b) 30 minutes after mixing.

As for the thermal setting time, increasing the NAC content from 0 to 1 wt.% would increase the setting time from 20.8 to 28.9 minutes, indicating that introduction of unreacted additives to PMMA reduces the local concentration of the PMMA oligomer and thus slows the curing speed (Xie et al., 2007b). Furthermore, more NAC content could cause hardness and difficulty in mixing and processing of the cement dough, as well as imperfections as a result of aggregation of load particles (Deb and Vazquez, 2001). A linear correlation between DC and setting time with different fractions of NAC at 10 minutes ($r=-0.9875$) and 30 minutes ($r=-0.9600$) is shown in Figure 6. As DC increased from 10 to 30 minutes with greater amounts of PMMA mixed into the NAC, a longer time was needed for polymerization. This may be also attributed to the influence of NAC on the polymerization of acrylic resin as additive is considered to create a heterogeneous system compared to that in a neat resin (Xie et al., 2007a).

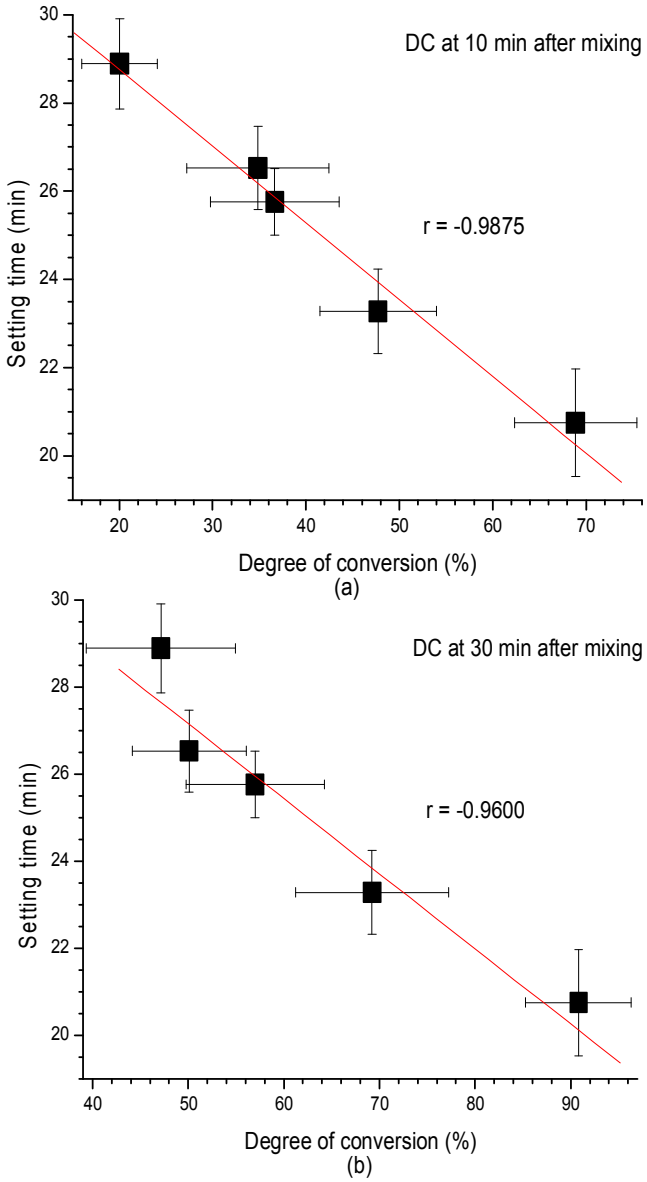


Figure 6. Correlation between degree of conversion and setting times of experimental PMMA bone cements: (a) 10 minutes and (b) 30 minutes after mixing.

While flexural strength is crucial and representative of a material's ability to resist deformation under load, surface hardness measurements can also quantify the endurance of acrylic materials. It can be seen in Table II that the microhardness values of each NAC-supplemented PMMA also increased over 7 days. Semi-log plots of correlations among DC and flexural strength and surface hardness at 2 hours (r=0.9108 and r=8180, respectively) and 7 days (r=0.9679 and r=0.8825, respectively) after polymerization are displayed in Figures 7 and Figure 8. Data revealed that the DC had a strong influence on the mechanical properties of PMMA bone cement, consistent with the opinion that microhardness results could be used as an indicator of the degree of polymerization in acrylic resin composite materials (Marghalani, 2010). There was a positive correlation between DC and mechanical performance. As the DC increased with different amounts of NAC, both the flexural strength and microhardness increased.

The flexural strength and surface hardness of PMMA bone cement are important for determining the successful long-term stability of dental prostheses after clinical application. It has been suggested that varying the chemical composition of bone cement has a significant effect on the DC and consequently on the mechanical properties of dental composites (Wu et al., 2010). The mobility of the monomer-chain can be restricted by the incorporation of fillers, leading to a decrease in the number of monomers and radical mobility, resulting in a low DC (Amirouche-Korichi et al., 2009). As for the flexural strength in Table II, the measured results of pure PMMA from two hours to 7 days all exceeded the minimum values stipulated by the ISO 5833 of 50 MPa for PMMA bone cement.

While the NAC-supplemented PMMA showed a lower flexural strength than pure PMMA after 7 days of incubation, the strengths of PMMA with 0.25 to 0.75 wt. % NAC all increased to 50 MPa. Thus, the incorporation of NAC into PMMA bone cement up to 0.75 wt. % would be clinical in terms of mechanical strength, and the effect on flexural strength may result in improvements in the longevity of the clinical practice.

Considering the limitations to our study, the results obtained here are entirely different from those of a previous study by another research group who stated that NAC-incorporation in bone cement led to no adverse effects on the thermal and mechanical properties (Tsukimura et al., 2009). This finding can be attributed to the following reasons. First, the chemical compositions of bone cements tested might have been different. The material properties of bone cements with different compositions vary, so similar bone cements need to be tested using commercially available bone cements (Belkoff et al., 1999). Second, in previous research, NAC was added to the MMA liquid before polymerization with PMMA powder. There is a possibility that pre-reaction of the monomer with NAC resulted in the formation of MMA/NAC adducts in the liquid monomer (Yamada and Ogawa, 2009), which may affect the thermal and mechanical properties. In our study, NAC was added to PMMA powder and then mixed with MMA, a sequence which may restrict the reaction between NAC and MMA in a short polymerization period.

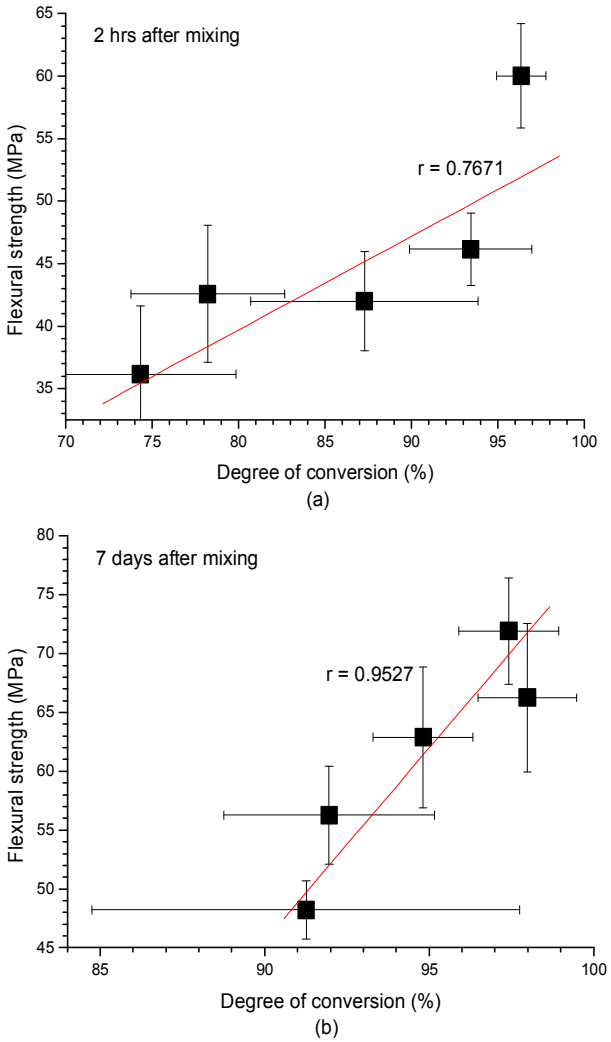


Figure 7. Correlation between degree of conversion and flexural strengths of experimental PMMA bone cements: (a) 2 hours and (b) 7 days after mixing.

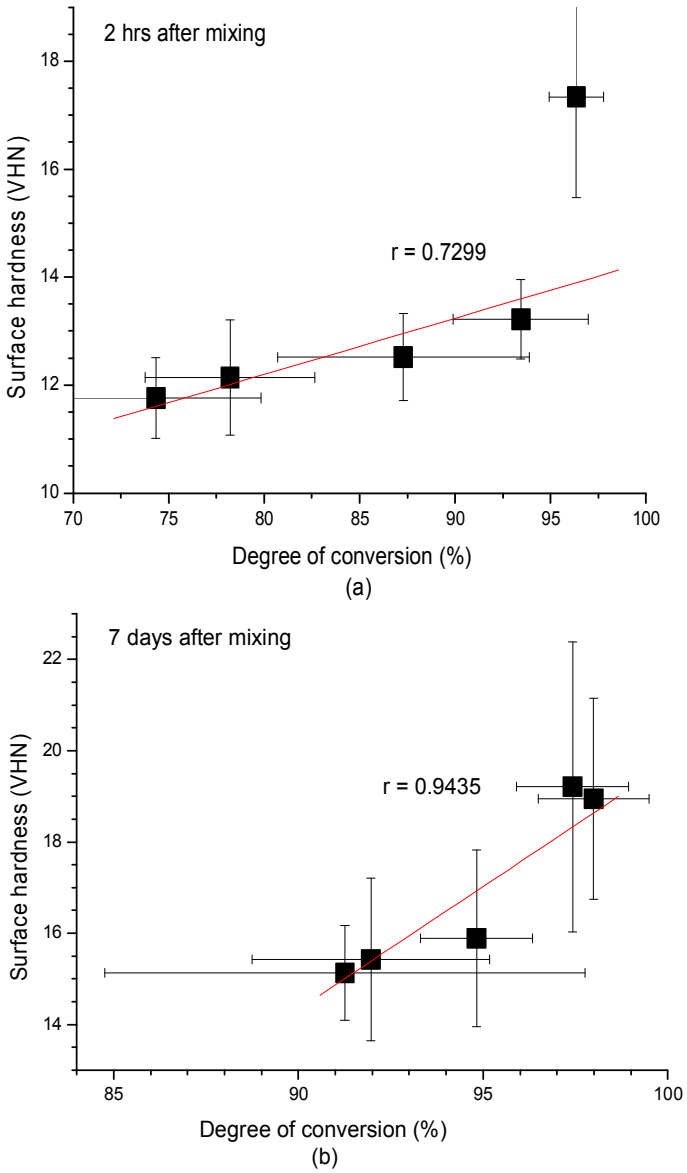


Figure 8. Correlation between degree of conversion and surface hardnesses of experimental PMMA bone cements: (a) 2 hours and (b) 7 days after mixing.

Since unreacted MMA leached from PMMA bone cement has adverse effects on oral tissues, the amount of released MMA in clinical use should be highly considered. Recently, the diffusion of residual monomer MMA from PMMA bone cement into water has been discussed in several studies (Gonçalves et al., 2008; Koroglu et al., 2012; Wady et al., 2011). It has been observed that the majority of residual monomers leach from the denture base within the first few days, with the maximal amount being observed in the first day.

The present study which used HPLC to determine the amount of residual MMA confirmed that significant leaching occurred within the first 24 hours of immersion for all tested PMMA bone cements, followed by longer lasting moderate leaching over the next 28 days. PMMA bone cement immersed after 20 minutes of mixing showed a relatively higher amount of released MMA than samples immersed after 40 minutes of mixing. Thus, it is recommended that acrylic resin be soaked in water after a longer mixing time and at least 24 hours before placement in the oral cavity so as to reduce the residual MMA and therefore the toxic potential of denture base resins.

In HPLC analysis, when NAC was incorporated at 0.25 wt.% or greater, the eluted MMA significantly increased. This phenomena was similar to the findings that the quantity of released MMA was higher in the fiber-reinforced PMMA-based composite than it was in pure PMMA bone cements (Mattila et al., 2006). Correlations between DC and residual monomer leaching from denture base polymers at two hours ($r=-0.9170$) and 7 days ($r=-0.9524$) after mixing are shown in Figure 9. The released MMA increased as DC decreased. Based on this information, with increased NAC addition, PMMA which released significantly

greater amounts of MMA also exhibited significantly lower flexural strength and surface hardness. This supports the result of earlier studies that measurement of mechanical properties is a simple way to predict DC and residual monomer content (Lee et al., 2002).

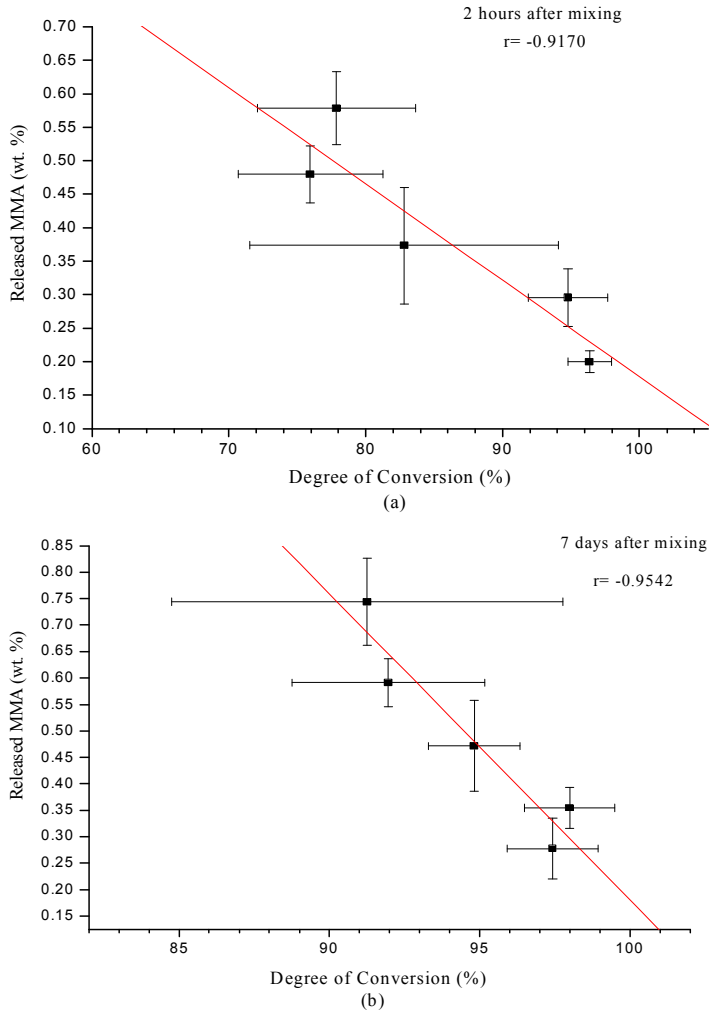


Figure 9. Correlation between degree of conversion and released MMA of experimental PMMA bone cements: (a) 2 hours and (b) 7 days after mixing.

Ⅵ. Conclusions

Within the limitations of this study, the results suggest that the addition of NAC into PMMA powders can reduce heat while maintaining acceptable mechanical properties. In this way, it is able to control the polymerization rate and avoid thermal damage to the neighboring tissues. With the longer setting time of NAC-supplemented PMMA, the surgeon would have more time to apply the bone cement. The released MMA can also be reduced by increasing the mixing time before immersion. There are good linear relationships between DC and thermal characteristics, mechanical properties and amount of released monomer.

It should also be noted that all specimens were prepared and tested at 23±1℃. Research demonstrated that a higher temperature increased the mobility of the molecules during the polymerization reaction. There is a possibility that the DCs and mechanical properties of the materials might be higher during the clinical application due to the higher body temperature (37±1℃). Therefore, different percentages of NAC in PMMA bone cement compositions can be considered as a subject for *in vitro* and *in vivo* applications.

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-국문초록-

N-acetylcysteine 첨가가 PMMA 골 시멘트의 중합에 주는 영향

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치과용 아크릴 레진은 구강내에서 잔류 메틸메타크릴레이트 (MMA) 등을 유출시켜 구강 조직내에 영향을 줄 수 있다. Thiol 계 항산화제인 n-acetylcysteine (NAC)은 sulfhydryl moiety 로 단량체 성분을 비활성화하여 PMMA 골 시멘트의 독성을 경감시킬 수 있다. 본 논문에서는 PMMA 분말에 NAC 를 0.25, 0.50, 0.75 및 1.00 wt. % 첨가하여 PMMA 골 시멘트를 적용할 경우 중합열, 중합정도 (DC), 기계적 특성 및 잔류 단량체 유출 등에 주는 영향을 알아보고자 하였다. 중합열, 경화시간, 굴곡강도, 표면경도, 단량체 유출량 등을 측정한 결과를 One-way ANOVA 와 Tukey multiple comparison test (p=0.05)로 통계 분석하여 다음의 결과를 얻었다.

1. 중합반응 중 PMMA 시멘트의 최고온도 (T_{max})는 유의하게 감소하였고, 경화시간 (t_{set})은 NAC 첨가량이 증가할수록 지속적으로 지연되었다.
2. FTIR로 PMMA 골 시멘트의 중합정도 (DC)를 측정한 결과 7일 경화 후 중합정도는 91% 정도를 보였다.
3. NAC 함량이 증가할수록 PMMA골 시멘트의 굴곡강도와 표면경도는 감소하는 양상을 보였으나, 시간이 경과 됨에 따라 다소 증가 하였다.
4. 증류수에 유출된 MMA 량을 HPLC 로 분석한 결과 증류수에 침지한 기간이 24 시간까지 증가함에 따라 유출량은 증가하였지만 그 이후에는 변화를 보이지 않았다.
5. PMMA 골 시멘트 실험군의 중합정도에 따른 MMA 유출량과 열 특성 및 기계적 특성과는 상관성을 보였다.

본 연구 결과 PMMA 골 시멘트 개발에 NAC 를 첨가시킬 경우 발열반응에 의한 문제를 다소 해결할 수 있으며, 생체적합성이 우수한 골 시멘트를 제시할 수 있을 것으로 생각한다.

주요어: PMMA 골 시멘트, n-acetylcysteine, 중합거동, 중합정도, 단량체 유출

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