REFERENCES

(1) A. N. Paruta and T. L. Breon, *J. Pharm. Sci.*, **59**, 1306(1970).

(2) E. Fisher and F. Dilthey, *Ann.*, **335**, 334(1904).

(3) "The Merck Index," 7th ed., Merck & Co., Rahway, N.J., 1960, pp. 71, 119, 794.

(4) A. N. Paruta, B. J. Sciarrone, and N. G. Lordi, *J. Pharm. Sci.*, **51**, 705(1962).

(5) A. N. Paruta, *ibid.*, **58**, 204(1969).

(6) S. A. Khalil and A. N. Martin, *ibid.*, **56**, 1225(1967).

(7) N. G. Lordi, B. J. Sciarrone, T. J. Ambrosio, and A. N. Paruta, *ibid.*, **53**, 463(1964).

(8) *Ibid.*, **53**, 1349(1964).

(9) L. Reber and C. Pathamanon, *Amer. J. Pharm.*, **139**, 234(1967).

ACKNOWLEDGMENTS AND ADDRESSES

Received February 19, 1974, from the *College of Pharmacy, University of Rhode Island, Kingston, RI 02881*

Accepted for publication May 21, 1975.

Abstracted in part from a dissertation submitted by B. Laprade to the Graduate School, University of Rhode Island, in partial fulfillment of the Doctor of Philosophy degree requirements.

[x] To whom inquiries should be directed.

Determination of Methyl Methacrylate in Surgical Acrylic Cement

ERIC B. SHEININ, WALTER R. BENSON [x], and WILSON L. BRANNON

Abstract □ A methyl methacrylate cement used in hip surgery as well as in dentistry was identified and quantitatively analyzed for its monomer content in starting materials and in the finished cement by proton magnetic resonance spectroscopy. IR data indicated that the monomer continued to escape from the product after it had hardened. The presence of 21% methyl methacrylate monomer relative to the polymer was demonstrated at the time the cement normally would be inserted into the body.

Keyphrases □ Methyl methacrylate—PMR analysis, ratio of monomer to polymer content, surgical acrylic cement □ Cement, surgical—PMR analysis of methyl methacrylate monomer relative to polymer content □ PMR spectroscopy—analysis, methyl methacrylate in surgical acrylic cement

The biomedical applications of polymers have increased rapidly in recent years (1, 2). One of the more widely used polymeric materials is methyl methacrylate bone cement. This polymer has been used extensively in dentistry and was approved for use in the United States for hip replacement and knee replacement operations. It is also used in skull surgery. Some deaths reported in 1971 during surgery prompted the examination of the material.

BACKGROUND

The methyl methacrylate cement is supplied as a kit made up of a sterile ampul of liquid and a sterile package of powder. The liquid consists of methyl methacrylate monomer, *N,N*-dimethyl-*p*-toluidine (polymerization initiator), and hydroquinone (polymerization inhibitor). The powder consists of polymethyl methacrylate–styrene copolymer (83.3%) and polymethyl methacrylate (16.7%) with benzoyl peroxide added as an initiator; preparations are available with or without barium sulfate (10%).

In the surgical application of the product, the liquid is mixed intimately with the powder until a putty is formed. This soft, workable putty is generally made into a ball and kept until just before being placed around the metal prosthesis. In this form, the prosthesis is placed in the body of the patient where the putty continues to harden.

Under normal surgical procedures, some monomer can diffuse out of the cement and into the body. It has been detected in the breath of patients undergoing this type of surgery. The high lipid solubility of the monomer aids its distribution throughout the body and makes hepatotoxicity a real possibility. This toxicity has been demonstrated in mice (3). In addition, extensive studies on dogs have shown large drops in blood pressure, decreases in heart rate, increased respiration, and changes in the ECG (4).

Sensitization to the monomer in humans has been reported (5–8); some investigators also suggested that it is responsible for, or a contributory factor in, observed cases of hypotensive states and cardiac arrest (4). In 1970, the British literature reported nine cases of cardiac arrest following the use of methyl methacrylate cement, and at least one fatality was reported in 1971 in this country (9).

There have been no definitive reports on the concentration of the potentially toxic monomer in the putty stage of the cement during the 4–5-min period after mixing when the putty is placed into the body of the patient. It was estimated that there may be up to 10% residual monomer in the curing mass after 1 hr (10). In a related study using a GLC method, Bechtel *et al.* (11), using the same product as that analyzed in the authors' laboratories, determined the amount of monomer leaching out of acrylic bone cements into tissues during polymerization. At 2 min after mixing, the monomer killed varying amounts of the surrounding tissue cells. However, the putty was placed in contact with the tissues earlier than the instructions indicated for the material used in that work. The monomer concentration in the putty at any time was unknown.

In 1971, Smith (12) reported the approximate composition of very similar acrylic cements used for dental applications, using an assay method based on the bromination of the double bond (13), and obtained 1.9 and 3.5% monomer content in acrylic cements used in hip replacement surgery. In these cases, the earliest reported analysis was obtained 1 hr after the kit contents were mixed. Methods based on IR spectrophotometry (14) and on polarography (15) have been used to determine the monomer content in bone cements sampled 1 hr or more after mixing.

The purpose of this investigation was to determine the amount of monomer, relative to the polymer, present in the putty at the recommended time of insertion into the body. Proton magnetic resonance (PMR) spectroscopy was used; this method requires no internal standard nor weighing of the sample, since the ratio of monomer to polymer is determined from the ratio of the vinyl to methoxyl signals.

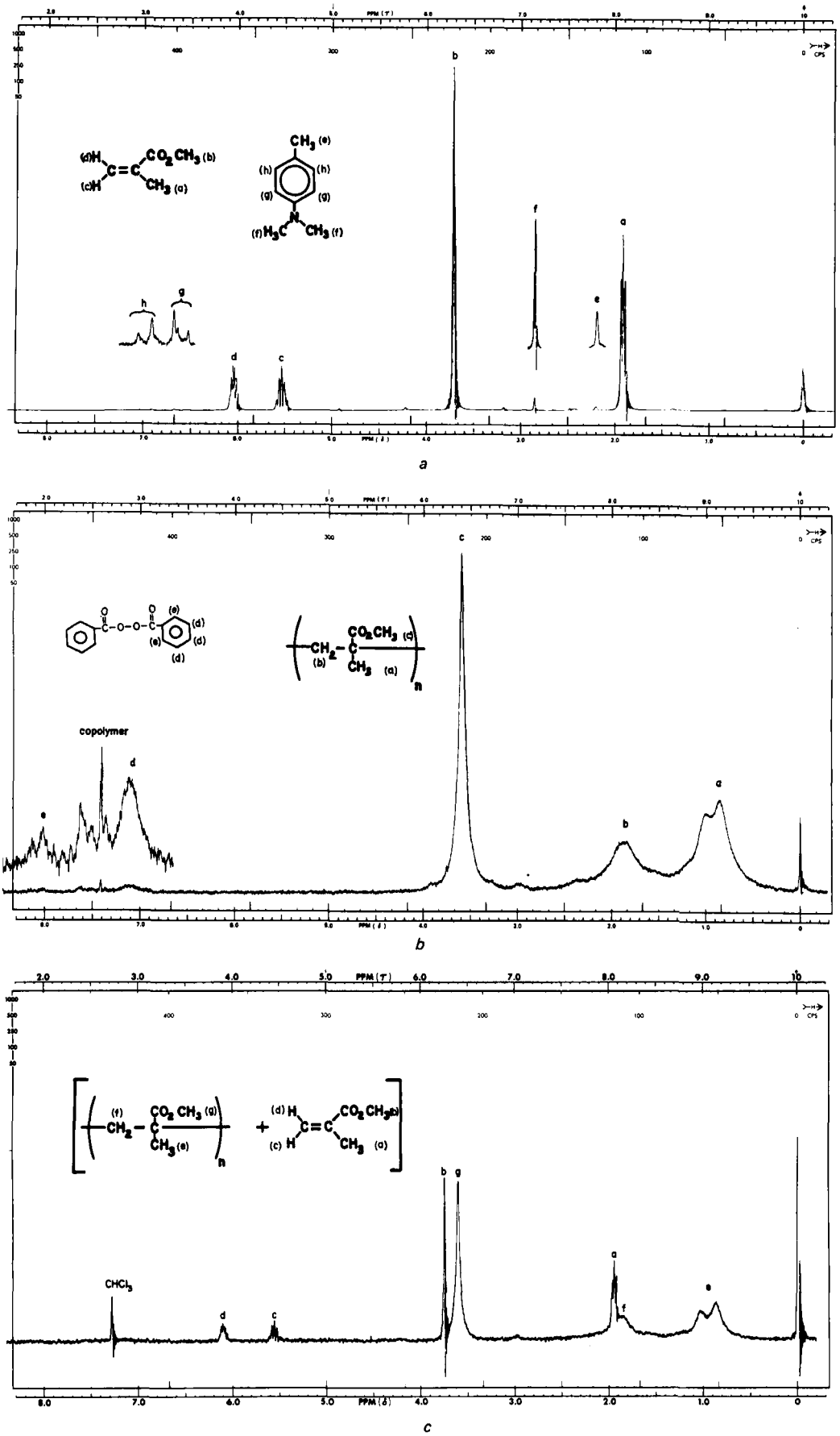

Figure 1—*PMR spectra of:* (a) *starting liquid (neat) consisting of methyl methacrylate and* N,N-*dimethyl*-p-*toluidine;* (b) *starting powder (in deuterated chloroform) consisting of polymethyl methacrylate, methyl methacrylate–styrene copolymer, and benzoyl peroxide; and* (c) *sample of the polymerizing mixture (in deuterated chloroform).*

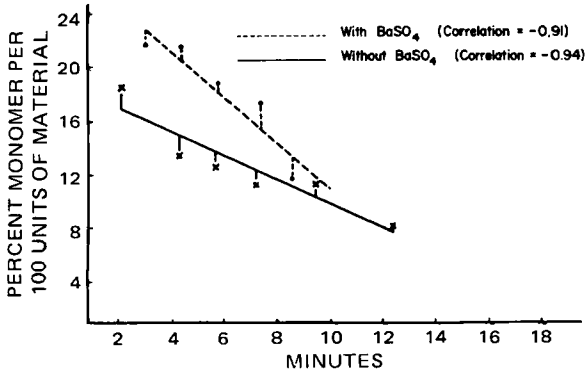

Figure 2—*Plot of the concentration of monomer found by PMR relative to the total amount of material* versus *time.*

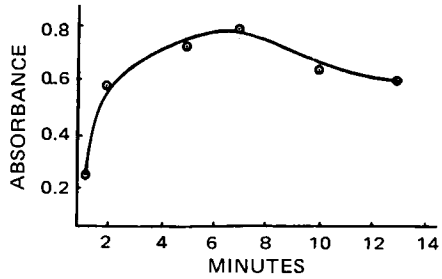

Figure 3—*Plot of the IR absorbance of a sample of the polymerizing mixture at 940.7 cm^{-1}* versus *time.*

EXPERIMENTAL

Instrumentation—A PMR spectrometer[1], having a six-turn insert, was used. Integrals were recorded by means of an automatic digital voltmeter[2]. An IR spectrophotometer[3] equipped with a small volume gas cell[4] was used for IR measurements.

PMR Analysis—Typically, the powder from one packet, 40 g (polymethyl methacrylate, 16.7%; methyl methacrylate–styrene copolymer, 83.3%; and a small amount of benzoyl peroxide), was placed in a mortar, and the contents from one vial, 20 ml (methyl methacrylate, *N,N*-dimethyl-*p*-toluidine, and hydroquinone) was added (this work was carried out in a well-ventilated hood). The resulting mixture was mulled with a pestle, with care to ensure that the liquid came in contact with all of the powder and that the mixture appeared to be homogeneous. When the material could be handled without sticking to rubber gloves, it was shaped into a ball and placed in a petri dish.

At intervals during a 2–11-min period after the initial mixing, small, thin samples (approximately 10 × 10 × 2 mm) were taken from the surface and placed into an erlenmeyer flask containing 2 ml of deuterated chloroform[5]. The flask was immediately stoppered, with care to ensure that the sample was in contact with the deuterated chloroform. Generally, five or six samples were used per experiment for the PMR determinations. After the sample had dissolved, the PMR spectrum was recorded and the integrals of the vinyl (δ 5.50–6.20)[6] and the methoxyl (δ 3.38–3.87) regions were determined in quintuplicate. (Figure 1*c* shows a representative spectrum.)

The percent of the monomer present in the total sample was calculated using:

$$\% \text{ monomer} = \frac{1.5 \times A_V}{A_M} \times 100 \qquad \text{(Eq. 1)}$$

where A_M = average of five determinations of the methoxyl integral, A_V = average of five determinations of the vinyl integral, and 1.5 = a conversion factor relating the number of protons in the vinyl region (two) to those in the methoxyl group (three).

Quenching of Polymerization by Solvent—To determine the effect of chloroform on the polymerization, 80.0 mg of the powder from a kit was dissolved in 0.5 ml of deuterated chloroform in an NMR tube[7]; 43.6 mg of the liquid was then added and the tube was stoppered and shaken. Twenty minutes later, the PMR spectrum was recorded and the integrals of the vinyl and the methoxyl regions were determined.

IR Analysis—At approximately 3 min after mixing, a small piece of putty was placed in the gas cell and the IR spectrum of the escaping vapor was recorded from 980 to 880 cm^{-1} every 1.5–2 min. In a separate experiment, another piece of putty was placed in the gas cell and the peak at 940.7 cm^{-1} was recorded at various intervals.

RESULTS AND DISCUSSION

Results at 4 min showed an average of 20.5 ± 2.25% of the monomer present in the putty for four determinations (range of 16–23%) using kits containing barium sulfate and an average of 14.6 ± 1.3% in the putty for five determinations (range of 13–17%) using kits containing no barium sulfate. These percentages decreased regularly until the surface of the mix was too hard to sample (10–12 min from the time of mixing) (Fig. 2). According to the package label, the putty is normally placed into the body 4–5 min after mixing is begun. The PMR spectroscopic procedure was equally applicable to either preparation.

Deuterated chloroform was chosen as the solvent for the PMR determinations because it quenched the polymerization reaction. Solutions of the polymeric powder and the monomeric liquid in deuterated chloroform were mixed together, as described under *Experimental,* to give a concentration of the monomer of 34.7%. After standing for 20 min, the monomer content was determined by the PMR procedure to be 34.6%, virtually identical to the known concentration within the limits of the measurement. This finding shows that polymerization of the monomer was effectively inhibited in chloroform, even in the presence of a catalyst. Since the dissolution of the polymerized product takes several hours, some further polymerization conceivably might take place within the sample mass during the dissolution period. Then the actual monomer content would be higher than the values reported here (Fig. 2).

The possibility was considered that depolymerization may take place in the deuterated chloroform solution, but it did not occur. When a sample of hardened material (approximately 2 weeks old) was dissolved in deuterated chloroform, the PMR spectrum did not show any changes over 1 week.

The integration accuracy of the instrument was shown by recording the spectrum of methyl methacrylate in deuterated chloroform and integrating the vinyl and methoxyl regions five times. The average value of the vinyl region was 102.1% of the average methoxyl integral after correcting for the number of protons in each region. This value agreed well with the original instrument specification of ±2%.

Several components in the starting materials can be identified by the PMR procedure. In the case of the liquid, the identification of both methyl methacrylate and *N,N*-dimethyl-*p*-toluidine is straightforward (Fig. 1*a*). The low level of hydroquinone used in the preparation could not be detected. When the powder was examined, the presence of benzoyl peroxide was detected (Fig. 1*b*). Quantitative analysis of the starting materials was not attempted during this investigation.

The starting materials from a similar preparation used in skull surgery were examined for comparison. The concentration of *N,N*-dimethyl-*p*-toluidine in the liquid of the second preparation appeared to be approximately half the amount observed relative to monomeric methyl methacrylate in the preparation used in hip surgery. The PMR spectra of the powder of the two preparations differed in the upfield region, indicating different tacticities of the polymers (16–18). These analyses indicate that PMR will distinguish between two starting polymers and show the relative amounts of starting materials in both liquid and solid.

[1] Varian A-60, Varian Associates, Palo Alto, Calif.
[2] Model 405BR, Hewlett-Packard Co., Palo Alto, Calif.
[3] Model 621, Perkin-Elmer Corp., Norwalk, Conn.
[4] A 7.5-cm path length; Perkin-Elmer Corp., Norwalk, Conn.
[5] Containing 99.8% deuterium, Stohler Isotope Chemicals, Rutherford, N.J.
[6] Chemical shifts are reported in parts per million downfield from tetramethylsilane.
[7] Catalog No. K-897205, Kontes Glass Co., Vineland, N.J.

The amount of the monomer present at the time of insertion is dependent on the mode of mixing. Even when the same operator mixed the putty every time, variations in the data were observed, both in the actual monomer content and in the slope of the resultant monomer *versus* time plot. (Figure 2 shows the plot of a representative experiment.) The slope varied from −1.5 to −1.7 for the preparation with barium sulfate and from −0.8 to −1.1 for the preparation without barium sulfate. Additionally, the length of time before the putty was completely set varied from 8 to 15 min.

The temperature of the bolus during polymerization reached 96° about 14 min after mixing, as determined by placing a thermometer in the bolus and recording the temperature at intervals. It has been reported (2) that this temperature is never approached in a surgical procedure because of the larger surface area of the mass used.

The authors have established that the monomer escapes at a rapid rate from the polymer bolus long after the bolus is too hard to take samples from it. The intent was to follow the rate of release of the vapor by gas phase IR spectrophotometry. However, when a piece of the putty was examined by IR beginning at approximately 3 min after mixing, the concentration of monomer in the gas cell increased for approximately 7 min and then began to drop slightly (Fig. 3). This drop was attributed to leakage of the monomer out of the cell or adsorption by the inner surfaces of the cell.

To distinguish between these processes, 4 μl of the monomer was placed in the cell; the intensity of the peak decreased with time and leveled off after 40 min. At this point, the sample was removed by purging the monomer vapor with dry nitrogen. Upon standing, the characteristics IR bands of the monomer reappeared and grew in intensity, indicating that the adsorbed monomer was coming from the walls and/or gaskets.

Polymerization of methyl methacrylate is initiated by the reaction between *N,N*-dimethyl-*p*-toluidine and benzoyl peroxide. No report was found that showed the fate of these catalysts. Because of their low concentrations in the finished product, the reaction of 10% solution[8,9] in deuterated benzene-d_6[10] was examined by PMR. Preliminary results indicated the possible presence of benzoic acid and 2,2′-(*N,N*-dimethylamino)-5,5′-dimethylbiphenyl[11]. Further work is needed to confirm these assignments and to identify other reaction products.

CONCLUSIONS

The high content (21%) of monomer in the putty about 4 min after the time of mixing was considerably higher than the previously published value (10) for the monomer content of the hardened cement after 60 min (1.9–3.5%). Since the recommended time of insertion into the human body is about 4 min and not 1 hr, any evaluation of the toxicity of the putty should be related to the 21% monomer value rather than the concentration after 1 hr. This conclusion suggests that further consideration be given to the effect of concentration of monomer in all commercial cement products upon the health of the exposed patients. This suggestion is based on the implication of the monomer in hepatotoxicity (9, 11) and on the reported deaths due to cardiac arrest attributed to the monomer (9).

[8] *N,N*-Dimethyl-*p*-toluidine was purchased from Eastman Organic Chemicals Division, Rochester, N.Y.

[9] Benzoyl peroxide was purchased from Fisher Scientific Co., Pittsburgh, Pa.

[10] Norell Chemical Co., Landisville, N.J.

[11] G. M. Brauer, National Bureau of Standards, Gaithersburg, Md., personal communication.

REFERENCES

(1) K. Kammermeyer, *Chem. Tech.*, **1**, 719(1971).

(2) J. Charnley, "Acrylic Cement in Orthopaedic Surgery," E. and S. Livingstone, London, England, 1970.

(3) *J. Amer. Med. Ass.*, **219**, 1143(1972).

(4) G. N. Mir, W. H. Lawrence, and J. Autian, *J. Pharm. Sci.*, **63**, 376(1974), and references therein.

(5) A. A. Fisher, *Cutis*, **12**, 333(1973).

(6) E. R. Kepes, P. S. Underwood, and L. Pecsey, *J. Amer. Med. Ass.*, **222**, 574(1972).

(7) B. Bentley-Phillips, *S. Afr. Med. J.*, **1970**, 1293.

(8) J. S. Pegum and F. A. Midhurst, *Brit. Med. J.*, **1971**, 141.

(9) C. A. Cohen and T. C. Smith, *Anesthesiology*, **35**, 547(1971).

(10) J. Wickstrom, Chairman, Committee on Biomedical Engineering, "What's Methyl Methacrylate?," American Academy of Orthopaedic Surgeons, exhibit by R. D. Keagy, J. Galante, and P. W. Mayer.

(11) A. Bechtel, H.-G. Willert, and H.-A. Frech, *Chromatographia*, **6**, 226(1973).

(12) D. C. Smith, *J. Biomed. Mater. Res.*, **1**, 189(1971).

(13) D. C. Smith and M. E. D. Bains, *J. Dent. Res.*, **35**, 16(1956).

(14) H. J. Caul, L. A. Wall, and N. Acquista, *J. Amer. Dent. Ass.*, **53**, 56(1956).

(15) R. J. Lacoste, I. Rosenthal, and C. H. Schmittinger, *Anal. Chem.*, **28**, 983(1956).

(16) P.-Q.-Tho, J. Mordini, and A. Guyot, *C. R., Ser. C*, **271**, 1294(1970).

(17) P.-Q.-Tho and J. Guillot, *J. Polym. Sci., A-1*, **8**, 2893(1970).

(18) I. R. Peat and W. F. Reynolds, *Tetrahedron Lett.*, **1972**, 1359.

ACKNOWLEDGMENTS AND ADDRESSES

Received April 15, 1975, from the *Division of Drug Chemistry (HFD-420), Food and Drug Administration, U.S. Department of Health, Education, and Welfare, Washington, DC 20204*

Accepted for publication May 27, 1975.

[x] To whom inquiries should be directed.