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The Acrylic Bone Cement in Arthroplasty

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Additional information is available at the end of the chapter

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1. Introduction

1.1. The genesis and evolution of acrylic bone cement

1.1.1. History

Otto Röhm is known as the developer of polymethylmethacrylate (PMMA) in 1901. Industrial-size chemical synthesis of MMA was achieved in the 1920s in the laboratories of Rohm and Haas, and the first biomedical applications of PMMA was the fabrication of dentures. In the 1930s it was discovered that the mixing of MMA monomer and benzoyl peroxide initiator with prepolymerized PMMA powder resulted in the formation of a dough-like material which could slowly harden into a glassy polymer. This two-component polymer (cement) was initially used to close cranial defects. Because of the transparency, strength, and stability of polymethylmethacrylate, the commercial production of cast sheets of it in the early 1930s led to its utilization as a denture base and prosthetic material. Originally pieces of the material were molded under heat and pressure.[1, 2, 3] In 1935, an injection molding technique was introduced by ICI for dentures in which the melted PMMA was injected into dried plaster molds under hydraulic pressure. These techniques proved to be too cumbersome. In 1936, as was mentioned above, it was discovered that mixing of methyl methacrylate monomer with the ground polymer produced a dough that could be shaped in plaster molds and could be polymerized into a solid mass by using benzoyl peroxide as a polymerization initiator. In the next few years, it was found that improved molding characteristics could be obtained using a powder that was a mixture of ground and spherical (bead) polymer particles.[1, 2]

The discovery of the dough molding technique led to the near universal use of these acrylic resins for dentures and prostheses for cranioplasties in the 1940s.[4] In 1943, German chemists discovered that if a tertiary amine such as dimethyl-pare-toluidine was added along with the benzoyl peroxide, the dough could be polymerized at room temperature. Based on this development, Kulzer and Degussa companies refined a dough-like, workable form of PMMA in 1943. Their developments led to the introduction of cold-cured PMMA, which hardens at room temperature. In the 1940s, with the advent of acrylic femoral hemiarthroplasties by Jean and Robert Judet, PMMA attracted interest in the field of orthopaedics. Kiaer and Haboush separately reported using PMMA to affix femoral implants in the early 1950s. The success with and the popularity of PMMA in orthopaedics is attributable to Sir John Charnley, whose work was affected by his exposure to the field of dentistry (because his father was a dentist) and his inherent interest in biomaterials. Charnley's early clinical accomplishments established a foundation for the continued use of PMMA in orthopaedics. Charnley had a long experience in producing his own instruments and gadgets. Charnley was interested in the work on thin sectioning of bones and rocks embedded in cast acrylic resin. He also performed a research into Judet prostheses and acrylic joints cast in alginate molds. He performed some arthroplasties with acrylic bone cement and reported the preliminary results of six cases in the British Journal of Bone and Joint Surgery in 1960. It is important to appreciate that this advance was not simply the use of acrylic cement but rather a conscious recognition of its ability to fill completely the medullary canal and adapt to the bone interface, so facilitating stress transfer, minimizing local stresses, and thereby stabilizing and anchoring the prosthesis. It was a new technique and provided the basis for the development of Charnley's concept of low friction arthroplasty during the next decade.[1, 2]

For over 40 years, poly(methylmethacrylate) (PMMA)-based bone cement, commonly known as acrylic bone cement, has been used for fixation of total joint replacement prostheses to periprosthetic bone. Today, most acrylic bone cements on the market consist of two components: a liquid and a powder one, which are mixed in the operating room until they become dough-like and are then applied to the bone prior to insertion of the component of the joint replacement prosthesis. The primary function of cements is to fix the joint replacement prosthesis to the periprosthetic bone tissue.[5] The basic component of acrylic bone cements is methylmethacrylate (MMA), which is an ester of methacrylic acid. In 1951, Kaier and Jansen in Copenhagen were the first to use PMMA bone cement for the fixation of acrylic cups to the subchondral bone of the femoral head. In 1953, Haboush used bone cement as a seating material for femoral head replacements without inserting it into the medullary canal. In 1958, Sir John Charnley used acrylic bone cement to fix femoral prostheses in the femur, as is done in modern-day joint arthroplasty these days. Charnley used a self-curing PMMA cement called Nu-Life, which was a pink-colored denture repair material. These early total hip replacements had a high incidence of failure, and it was not because of the cement or stems but because of the use of polytetrafluoroethylene (PTFE) acetabular cups. In 1966, CMW began to supply the first sterilized bone cement, formulated specifically for fixation of total joint replacement prostheses.[5] Nowadays, uncemented total hip replacement prostheses designs have largely been introduced in the orthopedic market, but acrylic cements continue to be one of the best primary methods of fixation of joint replacement pros-

theses, especially for knee replacement prostheses. In addition, injectable formulations of acrylic bone cements have been used for applications in vertebroplasty.

Several factors such as their chemical composition, viscosity, porosity, radiopacifiers and antibiotic additives, mixing methods, sterilization, temperature during handling, mechanical properties, and biocompatibility, affect the clinical performance of bone cements.

2. Composition and chemistry

The methylmethacrylate monomer consists of two carbon atoms that are covalently bound, with one of the carbon atoms covalently bonded to two hydrogen atoms and the other attached via a covalent bond to a methyl and acrylic group. Polymerization of MMA monomer produces PMMA, which is a polymer or a macromolecule. Hardened acrylic bone cement consists of linear, uncross-linked PMMA macromolecules of various lengths ranging from a few tens of thousands to a few million grams per mole. Acrylic bone cements comprise two components, often supplied in a 2:1 ratio: (a) a powder component, usually in a 40 g package, and (b) a liquid component, in a 20 mL ampoule.[2, 6](Table 1) There are several reasons for using a two-component bone cement instead of simply polymerizing pure MMA monomer:

The polymerization of MMA monomer is too slow and can take several hours or days, depending on the type and amount of reaction initiator used.

Pure MMA monomer has a very low viscosity and can easily diffuse into the blood stream, which can lead to cardiorespiratory and vascular complications.

The heat of polymerization can easily increase the temperature of the cement to over 100°C (boiling point for MMA = 100.3°C), which could lead to boiling of the volatile MMA monomer. The use of less amount of monomer and the presence of prepolymerized PMMA beads in the powder decreases the number of polymerization reaction and hence, the amount of released heat and assists in heat dissipation, decreasing the overall temperature.

After polymerization of pure MMA into PMMA, there would be a volumetric shrinkage of 21% due to differences in the density of the MMA monomer and the PMMA polymer. This amount of shrinkage is unacceptable and would lead to a large gap at the cement-bone and cement-prosthesis interface, compromising the fixation of the prosthesis.

The powder is the variable part in composition of bone cements among different brands, which contributes to differences in properties. (Figure 1) The powder component primarily consists of prepolymerized PMMA beads of 10 to 150 μm diameter, contributing to 83% to 99% of the powder. The prepolymerized beads of different bone cements include copolymers of MMA with styrene, methyl acrylate, or butyl methacrylate comonomers. The remaining components include a radiopacifier, either barium sulfate ($BaSO_4$) or zirconium dioxide (ZrO_2) (8% to 15% by weight), as well as an initiator, benzoyl peroxide (0.75% to 2.6%). The MMA monomer can self-polymerize under exposure to heat and light, but, this

reaction is very slow. Therefore, dibenzoyl peroxide (BPO) reaction initiator in powder form is included in the powder component. Other variations include the initiator tri-n-butylborane and accelerator 2,5-dimethylhexane- 2,5-hydroperoxide(in Bonemite, chlorophyll dye and ethanol and ascorbic acid. The initiator, radiopacifier, and antibiotic powders all consist of particles of approximately 1 μm in diameter. [7]

Constituent	Role
Powder components	
Polymer	Polymethylmethacrylate
Co-polymer (e.g. MA-MMA)	Alter physical properties of the cement
Barium sulphate or Zirconium dioxide	Radio-opacifiers
Antibiotics*	Antimicrobial prophylaxis
Dye (e.g. chlorophyll)	Distinguish cement from bone
Liquid components	
Monomer	Methylmethacrylate monomer
N,N-dimethyl-p-toluidine (DMPT)	Initiates cold curing of polymer
Benzoyl peroxide	Reacts with DMPT to catalyze polymerization
Hydroquinone	Stabilizer preventing premature polymerization
Dye (e.g. chlorophyll)	Distinguish cement from bone

*Plain bone cements do not contain antibiotics

Table 1. Commercial constituents of bone cement

The monomer, a colorless liquid with a characteristic odor, is packaged in ampules. The liquid components remain relatively constant among commercially available cements. 97% to 99% of this liquid consists of methylmethacrylate. N,N-dimethyl-para-toluidine (DMPT) makes up 0.4% to 2.8% by weight and acts as an accelerator to speed up the polymerization and setting of the cement. Since MMA can spontaneously polymerize during storage, addition of trace amounts of a stabilizer, usually hydroquinone (15 to 75 ppm), stabilizes and prevents premature polymerization of monomers.

MMA polymerizes by the mechanism of free radical polymerization, which consists of three steps: initiation, propagation, and termination. The initiation step involves decomposition of BPO monomer into radicals at room temperature.[7] (Figure 2)
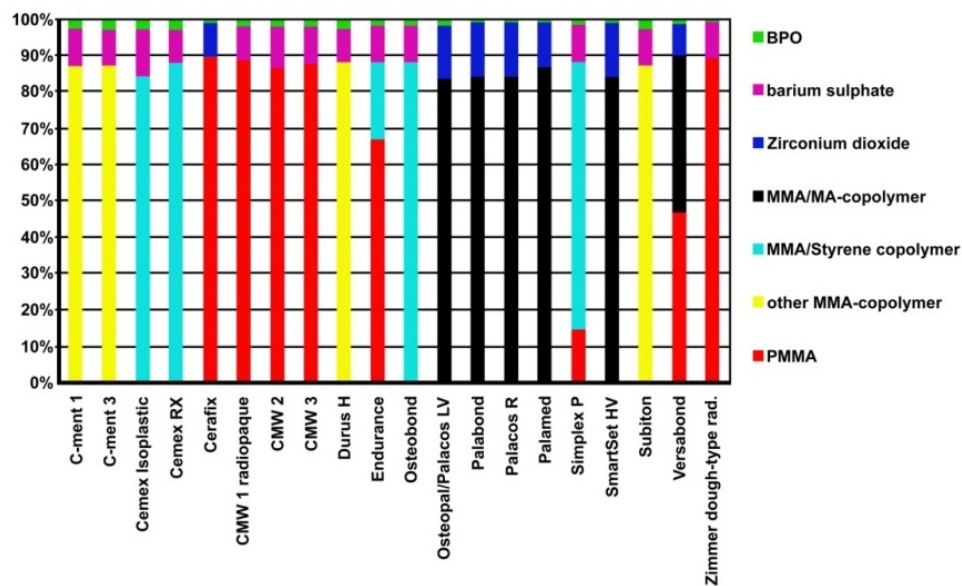
Figure 1. The composition of the powder of several PMMA bone cements on the market.
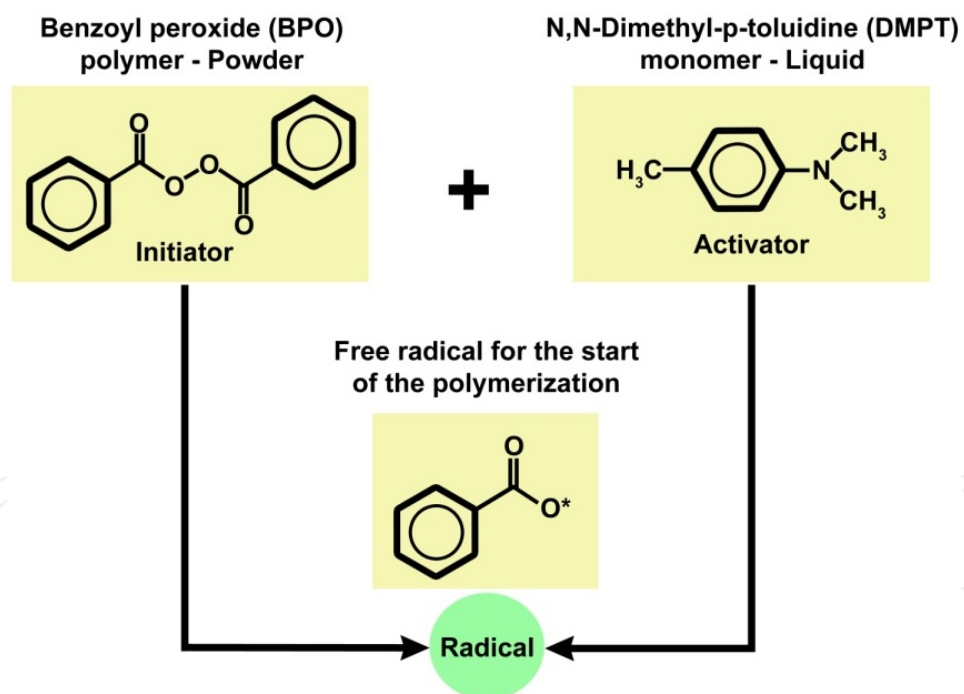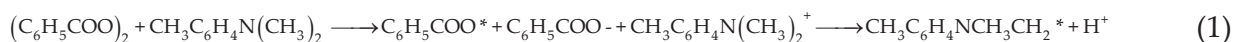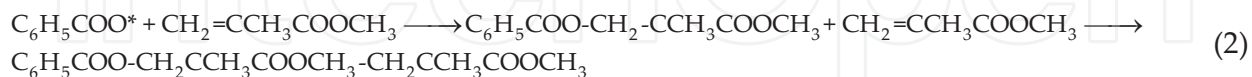

Figure 2. The initiation of the polymerization of MMA: BPO from the powder and DMPT from the liquid react to form radicals, starting the curing of bone cements.

Upon mixing of the two components, the DMPT in the liquid component decomposes BPO into a benzoyl radical and a benzoate anion as follows:

$$(C_6H_5COO)_2 + CH_3C_6H_4N(CH_3)_2 \longrightarrow C_6H_5COO* + C_6H_5COO - + CH_3C_6H_4N(CH_3)_2^+ \longrightarrow CH_3C_6H_4NCH_3CH_2* + H^+ \qquad (1)$$

where BPO = $(C_6H_5COO)_2$, DMPT= $CH_3C_6H_4N(CH_3)_2$, benzoyl radical = C_6H_5COO*, and benzoate anion = C_6H_5COO-.

The second step of the free radical polymerization is chain propagation in which the benzoyl radical reacts with the MMA monomer as follows:

$$C_6H_5COO* + CH_2=CCH_3COOCH_3 \longrightarrow C_6H_5COO-CH_2-CCH_3COOCH_3 + CH_2=CCH_3COOCH_3 \longrightarrow$$
$$C_6H_5COO-CH_2CCH_3COOCH_3-CH_2CCH_3COOCH_3 \qquad (2)$$

The free radical attacks one of the double bonds of the MMA monomer. One electron of the double bond pairs up with the electron of the free radical to form a bond between the oxygen of the benzoyl free radical and one of the carbon atoms of the MMA monomer while the second electron of the double bond shifts to the other carbon atom, which then turns into a free radical. This free radical then attacks another MMA monomer and the chain propagates until a PMMA of relatively high molecular weight, on the order of 100,000 to 1,000,000 g/mol, is achieved. Finally, chain termination can be achieved by chain coupling as follows:

$$-CH_2CXCH_3* + *CXCH_3CH_2- \longrightarrow -CH_2CXCH_3-CXCH_3CH_2- \qquad (3)$$

or, to a lesser extent, by disproportionation via transfer of a hydrogen atom as follows:

$$-CH_2CXCH_3* + *CXCH_3CH_2- \longrightarrow -CH_2C_XCH_2 + CXH=CH-¨ \qquad (4)$$
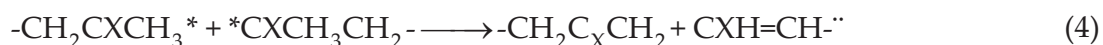
where X refers to the substituent $COOCH_3$.

The glass transition temperature of PMMA is about 105°C, but the glass transition temperature of hardened PMMA-based bone cement can be lower due to plasticization effects of residual monomer and water. With proceeding of polymerization, the growing polymer chains slowly turn into a hard, glassy material, and it becomes difficult for the monomer to diffuse through the hardened PMMA matrix to continue chain propagation. [8]

The hardened acrylic bone cement consists primarily of linear, uncross-linked PMMA macromolecules of various lengths, but their length (or molecular weight) can vary widely. The molecular weight of the hardened cement depends on several factors, such as (a) the molecular weight of the monomer used (usually MMA), (b) the molecular weight of the prepolymerized beads, (c) the ratio of the initiator and the accelerator, (d) the presence of stabilizers, (e) the ambient temperature during polymerization, and (f) the sterilization method.[7, 8]

3. Properties

3.1. Heat production during polymerization

Combining powder and liquid monomer initiates an exothermic reaction. In vitro, the peak temperatures reach 113°C. In vivo temperatures are reported to be between 40° and 56°C. Methylmethacrylate monomer, the basic building block of PMMA, contains carbon-carbon double bonds, which react with the free radical produced by the activator and initiator. The monomer free radical interacts with other monomer molecules, creating a growing polymer chain. During the polymerization, the powder changes to a workable dough. [7]

This reaction releases 52 KJ/mole of monomer, equating to heat production of 1.4 to 1.7×10^8 J/m^3 of cement. The production of heat by the curing cement has been studied *in vitro* and *in vivo* and modeled using finite element analysis. *In vitro* studies have shown that the thicker cement mantles, the higher ambient temperatures and the greater ratio of monomer to polymer the more heat is produced. Recorded temperatures range between 70°C and 120°C. Collagen denatures with prolonged exposure to temperatures in excess of 56°C, and the risk of causing thermal damage to bone has been emphasized by several authors. However, *in vivo* studies have recorded lower peaks of temperature. In 1977, Reckling and Dillon measured the temperature at the bone cement interface in 20 THRs. The maximum temperature was 48°C.[9] The reasons for the lower in vivo temperature are:

1. The thin layer of the bone cement

2. Blood circulation

3. The large surface area of the interface

4. Poor thermal conductivity of the cement

5. Heat dissipation to the prosthesis and to the vital tissue.

So, the temperature increase greater than the coagulation temperature of proteins is avoided.

Harving, Soballe and Bunger recorded temperatures above 56°C but only for two to three minutes. Even though, such temperatures may sometimes be reached, animal studies have shown no adverse effects. Nevertheless, concerns regarding thermal and chemical injury persisted.[3]

3.2. Curing of a bone cement

By mixing the powder and liquid, two different processes are started. First, the polymer powder takes up the monomer liquid, forming a more or less viscous fluid or a dough. This phenomenon is because of the swelling and dissolution processes of monomer and polymer powder. Swelling and dissolution processes are physical processes and they are important for the working characteristics of a bone cement. Second, a chemical process is initiated, which is responsible for the final hardening of the bone cement. The initiator BPO from the

polymer powder and the activator DMPT from the liquid interact to produce free radicals in the so-called "initiation reaction". These radicals are able to start the polymerization of MMA by adding to the polymerizable double-bond of the monomer molecule. This results in a growing polymer chain that builds up macromolecules. Because of the high number of radicals generated, many rapidly growing polymer chains are formed and, therefore, there is a fast conversion of MMA to PMMA. If two growing polymer chains meet, the chains are terminated by combining both, resulting in an unreactive polymer molecule. The polymerization of MMA is an exothermic reaction, resulting in a temperature increase in the curing bone cement.[7] This temperature maximum can be influenced by:

1. The chemical composition of the cement

2. By the powder to liquid ratio

3. By the radiopacifier.

3.3. Volume shrinkage

Because a polymerization means a conversion of a large number of monomer molecules to a much smaller number of polymer molecules, there is a volume shrinkage during curing of the bone cement. The reason for this shrinkage is the decreasing molecular distance between free monomer molecules before the polymerization and the molecular distance of the molecules bonded in the polymer chain. The volume shrinkage of pure MMA is approximately 21%. By using prepolymerized powder, the content of MMA in commercially available bone cements is reduced to approximately one third of the whole mass. The theoretic volume shrinkage of bone cements is therefore approximately 6%–7%. The real shrinkage is lower, however, because of the air inclusions in the cement dough. So, the real volume shrinkage of hand-mixed bone cement thus might be lower than the shrinkage of vacuum-mixed cement, because vacuum-mixed cement has hardly any air inclusions. Because acrylic bone cement absorbs water, its volume shrinkage is compensated by the expansion caused by the water-uptake.[8]

4. Processing and handling of bone cement

The handling characteristics and setting times of acrylic cements are of great importance for orthopedic surgeons. The handling of bone cements can be described by four different phases with their corresponding viscosities:

1. The mixing phase (up to 1 minute) is the period during which the powder and the liquid are homogenized thoroughly. The powder and the liquid can be mixed manually by using a bowl and a spatula or by a special mixing system, applying vacuum to avoid the formation of voids.

2. The waiting phase (up to several minutes, according to the type of cement and the handling temperature) is the period to reach a non-sticky state of the cement.

3. The working phase (2–4 minutes, according to the type of cement and the handling temperature) is the period during which the surgeon can inject the cement and insert the prosthesis. The viscosity of the cement has to be high enough to withstand the bleeding pressure. Blood pervasion of the cement results in a reduction of the strength of the cement. A late application at a too high viscosity level may result in poor interfaces between the prosthesis, the cement, and the bone.

4. The hardening phase (1–2 minutes) is the period of the final setting process and the development of the polymerization heat.

The effect of the temperature on the length of the phases is clearly visible. The information given by the temperature versus time curves of different cements is not always comparable, because manufacturers use different determination methods resulting in variant lengths of the working phases. This disagreement is caused by the lack of a universal detection method. A wide experience and knowledge by the surgeon is therefore helpful to find the optimal range of time to inject the cement and to fix the prosthesis. The method described in ISO 5833 and ASTM F 451 to determine a viscosity-like parameter is the intrusion test. This is not really a test method for the determination of the true viscosity. To perform this test, the mixed cement is placed in a plastic mold and is loaded with a force of 49 N for 1 minute. The depth of the intrusion of the cement into four drill holes is measured. This method is only available for high viscosity bone cements. In the standard ASTM F 451, there is another extrusion viscosity test described with a capillary rheometer for low viscosity bone cements. [7]

In the Standards, there are two further time parameters defined: the doughing time and the setting time. The doughing time end by the beginning of the working phase and it is determined by recording from the start time of mixing until the mixture is able to separate cleanly from a gloved finger. The second time parameter is the setting time, which is defined as the time to reach a temperature midway between ambient and maximum. The end of setting time marks the final hardening of the bone cement. [8]

During the waiting period swelling of the beads occurs and allows the polymerization to proceed, leading to an increase in viscosity. At this stage, the cement turns into a sticky dough. The working period begins when the cement is no longer sticky but of sufficiently low viscosity to permit the surgeon to easily apply the cement into the prepared place. During this period, the chain propagation continues, along with an increase in viscosity. The viscosity of the cement must be carefully assessed before inserting the cement because with a very low viscosity the cement would not be able to withstand the bleeding pressure. This would result in blood lamination in the cement, which can weaken the cement. The heat produced during this period, results in thermal expansion of the cement. On the other hand, there is a volumetric shrinkage of the cement as the MMA monomer converts into the denser PMMA polymer.

The final stage is the hardening period, when the polymerization terminates and leads to a hardened cement. The temperature of the cement continues to elevate during this period and then slowly decreases to body temperatures. During this period, the cement undergos volumetric shrinkage along with thermal shrinkage as the cement cools down to body temperature. While the manufacturer can determine the hardening period length using in vitro

measurements at a controlled temperature and humidity in a laboratory environment, it is difficult to predict the hardening period in vivo, with accuracy due to variations in the ambient environment in the operating room, the body temperature, and thickness of the cement mantle, all of which can alter the setting times of the cement. Several factors, such as the type of mixing method used, the viscosity of the cement, the precooling of the monomer and/or powder, the preheating of the powder component, and the preheating of the prosthesis, can also significantly alter the times of some of the handling phases. Thus it is important for the surgeon to know each of the factors that can alter the duration of each phase. [7]

4.1. Viscosity and handling properties

The dynamic viscosity (η) of fluids is denoted by shear stress (F)/shear rate (S) [η = F/S]. Fluids are designated as Newtonian if shear stress is linearly related to shear rate. Cement in its liquid phase of curing behaves as a non-Newtonian fluid with viscosity decreasing as shear rate is increased. This is called pseudoplastic or shear thinning behaviour. However, the viscosity of all cements increases during polymerisation as the polymer chains lengthen.[10]

The mixed cement begins as a viscous liquid, then turns into a viscoelastic material, and finally hardens into a predominantly elastic solid. Thus, it is important to monitor both the dynamic viscosity as well as the viscoelastic parameters, such as storage modulus (G'), loss modulus (G"), and tanδ (their ratio). A high storage modulus indicates that the material is more solid-like whereas a high loss modulus shows that the material is more viscous.[7]

The viscosity of bone cements at the dough stage is determined mainly by the chemical composition and the powder to monomer ratio. These aspects should never be modified in the operating theater to modify the viscosity. There are some methods to modify the viscosity without changing other characteristics of the cement, however. One of them is the prechilling of the cement. The velocity of the reaction, and with it the viscosity, depends on the temperature. Prechilling of cements, especially of high viscosity cements, has been introduced with the introduction of mixing systems to make mixing of cement in these systems more convenient and to improve the quality of the mixture, especially with respect to porosity. [8]

Another method for applying this change is preheating the cement, to accelerate the polymerization and thus, reducing the operation time. But it has been shown that by this heat application to the cement powder, various characteristics of the cement itself or the cemented construct are either enhanced, degraded, or marginally affected, which depends on the structure of the cement powder and its stability against the heat. Specifically, these properties are significantly decreased when the principal constituent in the powder has a low resistance to degradation by the preheat temperature (as is the case of the PMMA polymer in Cemex XL and CMW 1 cements) but are not when the resistance is high (as in the case of a mixture of PMMA + MMA styrene copolymer in Surgical Simplex P cement).[11]

Manufacturers can also change the viscosity of cement by changing the molecular weight, by using co-polymers, and by varying the methods of sterilization. In addition, the curing process itself can be controlled by altering the proportions of the initiator (Toluidine) and the monomer, and this can change the working properties.

The cement must be liquid enough during the working phase to be forced through a delivery device and then flow under pressure to penetrate the interstices of cancellous bone, achieving micro-interlock. Bone cements are usually divided into three categories: high, medium and low viscosity:

Low. These have a long waiting phase of three minutes, also known as a sticky phase. The viscosity rapidly increases during the working phase and the hardening phase is one to two minutes long.

Medium. There is a long waiting phase of three minutes, but during the working phase, the viscosity only increases slowly. Hardening takes between one minute 30 seconds, and two minutes 30 seconds.

High. A short waiting/sticky phase is followed by a long working phase. The viscosity remains constant until the end of the working phase. The hardening phase lasts between one minute 30 seconds and two minutes. High viscosity cements are therefore forgiving for the surgeon and are in predominant use in orthopaedics. [3]

However, the rates of curing are very sensitive to environmental factors. Low ambient temperatures during storing and mixing, and high humidity both prolong setting time. Typical representatives of high viscosity cements are Palacos R (Biomet Inc.; Warsaw/USA; Schering-Plough; Heist-op-den-Berg/Belgium; Heraeus Kulzer; Wehrheim/Germany), Palamed (Biomet Merck; Ried/Switzerland; Heraeus Kulzer), CMW 1 (DePuy; Blackpool/England), Simplex P (Stryker; Limerick/Ireland), and Cemfix 1 (Teknimed; Vic en Bigorre/France), whereas Osteopal (Biomet Merck; Heraeus Kulzer), Palacos LV (Schering-Plough; Heraeus Kulzer), Osteobond (Zimmer; Warsaw/USA), Versabond (Smith & Nephew; Memphis/USA), Cemfix 3 (Teknimed), Sulcem 3 (Zimmer; Baar/Switzerland), and CMW 3 (DePuy) are examples of low viscosity cements. [7]

The high viscosity during mixing might be a disadvantage, because this supports the entrapping of air. The viscosity is the most important handling property for the surgeon and determines the working properties of the cement.

4.2. Residual monomer and monomer release

Radical polymerization of the MMA in bone cement generally does not proceed to completion, because the mobility of remaining monomer molecules is inhibited at high conversion rates. There will remain, therefore, some residual monomer. Directly after curing, the content of residual monomer is approximately 2%–6%. In the following 3 weeks this content decreases to approximately 0.5%. The main part (approximately 80%) of the total residual monomer is post-polymerized slowly. A smaller part of the residual monomer is released from the cement and metabolized to carbon dioxide and water in the citric acid cycle.(Figure 3) In earlier times, released MMA was considered the main reason for perioperative respiration and circulation upset. However, these effects are definitely the result of the increase in the intramedullary pressure and fat embolism. They are not caused by the residual monomer. [7]
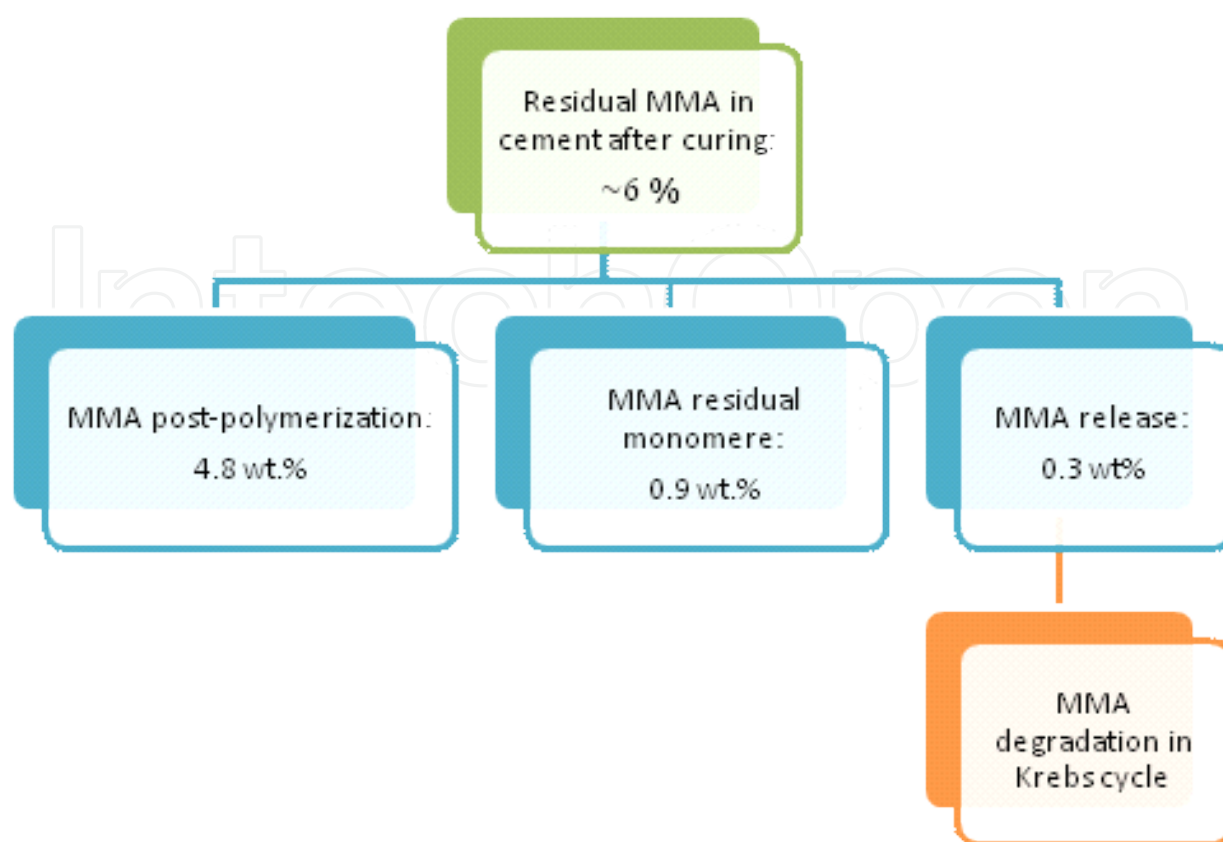
Figure 3. Residual monomer in acrylic bone cement: post-polymerization and release with subsequent degradation.

4.3. Radiopacity

After a total joint replacement, if the cement does not have a distinct opacity, the surgeon cannot monitor the healing process clearly. This is the reason why radiopaque materials are added to bone cements, so the hardened cement is radiopaque. Barium sulfate or zirconium dioxide is used as opacifiers in all available bone cements.(Figure 4) The radiopacifier does not contribute to the polymer chain. It is dispersed uniformly in the polymer powder and in the resulting solid bone cement. Animal experiments and in vivo studies with different cell cultures showed more osteolytic changes by using barium sulfate than by using zirconium dioxide. Despite the low solubility of barium sulfate, toxic barium ions can be released. On the other hand, the abrasive properties of zirconium dioxide seem to be a disadvantage. All bone cements examined contain 8.0%–15.0% opacifier within the polymer. Zirconium dioxide provides higher opacity to bone cements compared to barium sulfate. Bone cements with more than 15.0% zirconium dioxide in the polymer have the most distinct opacity.[2, 3, 7]

4.4. Molecular weight and sterilization

The molecular weight of the polymer powder particles is affected strongly by the sterilization procedure used. Sterilization by γ-irradiation or β-irradiation significantly lowers the molecular weight, whereas sterilization by ethylene oxide has no influence on the molecular

weight of the polymer. The molecular weight influences the swelling properties and the mechanical properties of the bone cement; therefore, low molecular weights have a few disadvantages. Sterilization by ethylene oxide is the preferred method for bone cements, because there is no change in material properties during sterilization. [12]
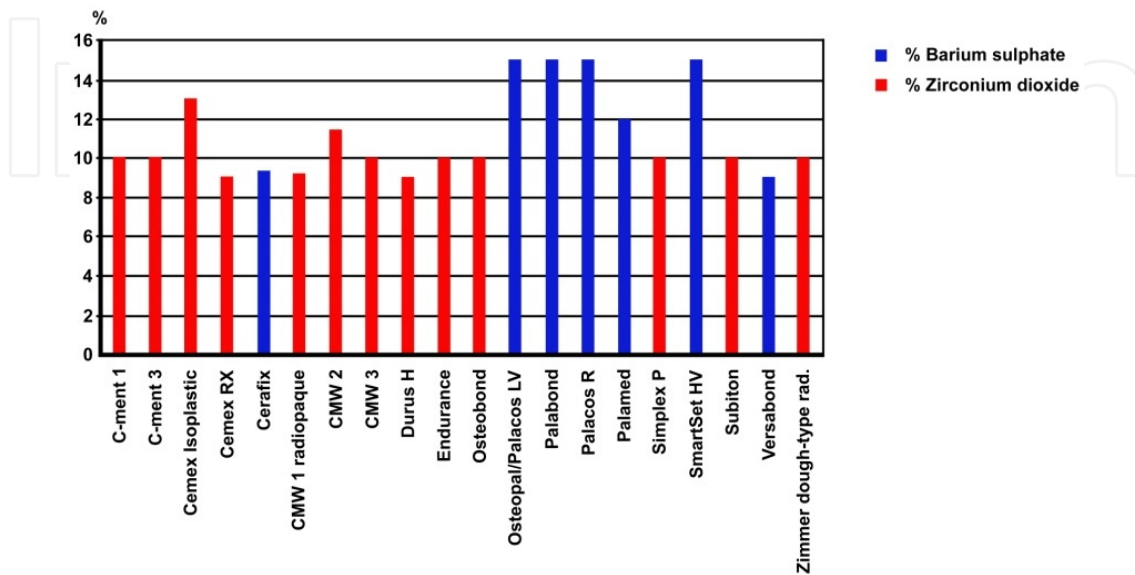

Figure 4. Content of radiopaquer in the powder of several acrylic bone cements; two radiopaquer agents are used in commercial products: Barium sulfate and Zirconium dioxide.

5. Cement morphology

The composition of hardened cement consists of prepolymerized beads of PMMA or their copolymers fused with the polymerized MMA monomer, in addition to radiopacifiers and additives, such as powders of antibiotics, as well as pores or voids and residual initiator. These parts of a cement composition act as flaws. These flaws can be due to: (a) air dissolved within the powder particles; (b) air entrapment during mixing of powder and liquid monomer; (c) incomplete fusion of prepolymerized PMMA beads with the setting MMA; (d) evaporation of the volatile monomer due to the heat of reaction during setting; (e) air entrapment during transfer of the dough to the gun; and (f) air entrapment during introduction of cement into the medullary canal. The major problem associated with the presence of flaws is that when a critical flaw size is achieved, the flaws act as sites of stress concentration, leading to weakening of the cement. But if the critical flaw size is not reached, they act as crack blunting part of the cement upon its fracture. In other words, the cracks deviate from their path when they encounter flaws in their path associated with pores and radiopacifier particles. The Griffith crack criterion assumes that there exists a critical flaw size unique to each material above which its fracture strength is compromised. For PMMA, the critical flaw size is 70 μm. Thus, if the pores are smaller than the critical flaw size for PMMA, the porosity will not compromise the fracture strength of bone cement. It is general-

ly well known that hardened bone cement contain macropores (pore diameter greater than 1 mm) and micropores (pore diameter 0.01-1.0 mm). Based on the Griffith theory, elimination of the macropores would be more important than elimination of the micropores, especially the pores much smaller than 70 μm in diameter. The most common method of eliminating pores is to use centrifugation and vacuum mixing methods. Another source of flaws that can be potential sites of high stress concentration is radiopacifier powder particles. A radiopacifier powder, usually barium sulfate or zirconium oxide, consists of particles with a broad range of sizes, from approximately 0.2 to 2 μm in diameter. Zirconium oxide is a harder material than barium sulfate. Thus, if there is loosening, there could be concerns with regards to third body abrasive wear in the bearing surface of the joint replacement. Barium sulfate is generally insoluble, but there are concerns about toxicity of barium ions. Poor spread of radiopacifier particles in the region between the prepolymerized cement beads can affect both crack initiation and crack propagation, especially if they are larger than the critical flaw size for PMMA. The radiopacifier particles do not bond with PMMA and instead reside within pores, which are larger than these particles due to cement shrinkage. [13, 8]

6. Mixing techniques and its effect on porosity

Mixing techniques are of great importance in determining the content and size of flaws that can affect the cement toughness. Historically, three methods of mixing of cement have been employed: (a) hand mixing in air; (b) hand mixing followed by centrifugation; and (c) hand mixing in an evacuated mixing device, commonly known as "vacuum mixing." [8, 14]

Hand mixing involves mixing of the liquid and powder components in an open bowl using a spatula at a speed of 1 to 2 Hz for a period of duration of approximately 2 minutes. The hand-mixing method can introduce a porosity of 7% or higher. It is confirmed that excessive mixing can lead to increased porosity. By decreasing the number of beats and waiting for a short duration after wetting the powder component with the monomer the porosity of cement can be reduced to approximately 5%. Centrifugation was later introduced as a method to eliminate pores. In this method, the liquid and powder components are initially hand mixed and then placed in a tube and subjected to centrifugation at a speed of 2300 to 4000 rpm for a duration of 0.5 to 3 minutes. With this method the total porosity decreases to 1% or less, which is significantly lower than the porosity observed in hand mixing. It is obvious that for centrifugation to be effective, the viscosity of the cement must be relatively low, allowing the air bubbles to flow to the surface of the cement under the centrifugal force. One way to assist centrifugation is to chill the MMA monomer prior to mixing. One potential disadvantage of the centrifugation mixing technique is that it can lead to an inhomogeneous distribution of radiopacifier particles in the centrifuged cement, due to the difference in density of radiopacifier particles and PMMA and MMA monomer. The third type of mixing technique is vacuum mixing, in which the two components of bone cements are placed in a mixing bowl and are mixed after subjecting the bowl to vacuum conditions. The vacuum-mixing devices have proven to substantially decrease porosity in cements to less than 1% and consequently to increase their fatigue properties. Another major reason for using vac-

uum mixing is that MMA monomer is contained within the mixing bowl, which limits exposure to its vapors. Toxicology information obtained from materials safety data sheets (MSDSs) show that MMA monomer is harmful if inhaled, swallowed, or absorbed through the skin. [8, 14]

It must be noted that this reduction in the porosity of cement mantle with vacuum-mixing, is not always the case. Messick et al found that vacuum-mixed cement does not result in overall lower porosity of the cement, but the distribution of porosity may be different when compared with that of hand-mixed cement.(Figure 5) It has also been demonstrated that very high vacuum levels can be associated with the presence of cracks in the cement.[15]
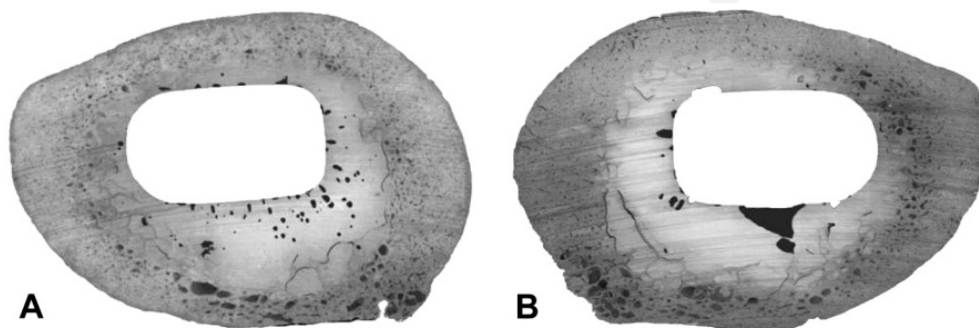

Figure 5. Representative sections illustrating the distribution of porosity for A) hand- and B) vacuum-mixed cement.

7. Mechanical and physical properties

7.1. Static mechanical properties (Table 2)

The main function of acrylic bone cement is the stable fixation of endoprostheses. The cement must endure considerable stresses, thus, sufficient strength is one of the most important demands to achieve a stable fixation and to guarantee long-term stability of the implant. The cement layer has the effect of an elastic buffer between prosthesis and bone. Because of its close adaptation to bone and its viscoelastic properties, it can reduce the stress concentrations at the interface with the bone. In the end, transferring load from the prosthesis to the bone as efficiently as possible also is decisive for the long-term stability of the implant. The mechanism of loading is especially complex for hip arthroplasty; therefore, it is difficult to define what sufficient strength actually means. The total load affecting bone cement is a mixture of compressive loading combined with bending, tension, shear, and torsion. It has been extremely difficult to simulate this complex situation in the laboratory. Two mechanical tests have been introduced into ISO 5833, the relevant standard for testing acrylic bone cements. These tests are the compression and the four-point bending test for the determination of the compressive strength, the bending strength and the bending modulus (modulus of elasticity or Young's modulus), respectively. The standard ASTM F 451 includes the compression test only. Generally there are two different fundamental measuring principles to

determine mechanical properties of bone cements: applying static (also called quasistatic) stresses and dynamic stresses. Static tests are destructive tests with a uniaxial single loading, increasing until failure, in contrast to dynamic tests that involve a cyclic loading.[16]

The compression test according to the standards ISO 5833 and ASTM F 451 is a static method in which the compressive strength is defined as the maximum stress that a material can withstand before failure in compression. The test is executed with a universal testing machine equipped to record load versus crosshead displacement. The minimum requirement for the compressive strength is 70 MPa according to the standards. All commercial antibiotic and plain bone cements meet this requirement. Between both cement types, no significant differences in compressive strength are observable.[10]

The second mechanical test according to ISO 5833 is the four-point bending test, also performed with a universal testing machine. According to ISO 5833 the minimum requirement for the bending strength is 50 MPa and for the bending modulus it is 1800 MPa, respectively. Again, all commercial cements clearly fulfill the requirements. The addition of antibiotics reduces the bending strength, but the differences between antibiotic and plain cement are not always statistically significant. The bending modulus represents the ratio of stress to corresponding strain of the material within the elastic range characterizing the relative stiffness of the material. Stiff materials have a high modulus, eg, glass and ceramics; ductile materials like rubber have a low modulus. Within the elastic range the stress and strain are directly proportional following Hooke's Law, and if the load is released, the material regains its initial dimensions. The elastic range is limited by a stress limit, the so-called ''proportional limit'' at which the physical properties of the material actually change and the material might not recover its initial shape after releasing load. As already mentioned the cement acts as a mechanical buffer. For this purpose the modulus of elasticity of bone cement has to be lower than the moduli of the metallic prosthesis and the bone. The modulus must not decrease to below a minimum value, however; therefore, a lower limit for the modulus is established in ISO 5833. The modulus varies with temperature, which means the higher the temperature, the lower the modulus. Testing bone cement at 23°C is not a really convenient way to get meaningful results for the application in the human body. The mechanical performance of bone cements is influenced by various parameters, such as composition of the cement, porosity, and preparation of the cement. The addition of radiopacifier and antibiotics to a bone cement slightly decreases the mechanical strength. These additives are necessary to get radiograph opacity and antibiotic protection of the implant, which are important attributes of bone cements. Despite these additives, the resulting cements easily meet the requirements. [16,17]

Although bone cement has a high compressive strength, it is susceptible to fracture that might result from tensile loading. Tensile tests therefore are performed according to ISO 527-1 or ASTM D 638. These standards describe a static test method applicable for all polymer materials. The uniaxial tensile test is executed with flat tapered specimens. The ultimate tensile strength is defined as the maximum stress that a material can withstand before failure in tension. The tensile strength is approximately 50 –60 MPa and there are no significant differences between the tested materials. Again, the addition of antibiotics seems to reduce

the tensile strength, but the differences between antibiotic and plain cement are not statistically significant. [18]

The compressive strength of bone cement is higher than the flexural strength and that is higher than the tensile strength. This descending order is found in all polymer materials. That means tensile loading may be a higher risk factor for failure than compressive loading. In vivo, simple tensile loading, however, does not play an important part in reality; complex combinations of different loading types are more relevant. From a physical point of view, bending is a mixture of compressive and tensile loading; therefore, the bending test actually is a realistic test. [17]

One further static test applied with bone cements is the shear strength test according to ASTM D732. This mechanical parameter is important because debonding of the stem–cement interface has been implicated in the initiation of failure of cemented femoral stems. The interface static shear strength is influenced by surface roughness, cement type, and porosity. Surface finish has the greatest effect on the interface strength. Increasing the surface roughness increases the interface shear strength. Increasing the surface roughness to greater than a certain value, however, has no additional affect. Cement type and porosity have a minor influence on the static interface strength. [19]

Furthermore, there are methods to determine fracture properties, such as fracture toughness (ASTM E399 and ISO 13,586) and impact strength (ISO 179/ISO 180/DIN 53,435). There is a correlation between the two methods. For a given specimen configuration, g-irradiation produced a statistically significant decrease in fracture toughness because of the concomitant depreciation in molecular weight. Impact strength is a measure of the energy required to cause a material to fracture when struck by a sudden blow. The addition of radiopacifier and antibiotics together with pores in the cement might have a negative effect on the impact strength. [20]

7.2. Water uptake and glass transition

When considering the mechanical tests described previously, one fact should be taken into account: most of the tests are executed with dry specimens at room temperature. The cement has to perform its task in the human body, however, in contact with body fluid and at a temperature of 37°C. Mechanical properties of polymers vary relative to their temperature and water uptake. The absorption of water results in a lower modulus of elasticity and in a less stiff material. The decreasing stiffness may even be advantageous for fracture resistance and long-term stability of the implant. The water uptake of commercial bone cements is approximately 1%–2% for plain bone cements and slightly higher for antibiotic bone cements. There is high initial water uptake during the first days of incubation at 37°C. The bone cements are completely water-saturated 4–8 weeks after incubation. The glass transition temperature is a physical parameter defining the softening range of a material. Softening means a transition from a hard and rigid glassy state with a high modulus to a soft rubbery state with a low modulus by heating the polymer. If the material for anchoring endoprosthesis is in the rubbery state, there would be a high risk for subsidence of the femoral stem and no stable fixation of the implant would be possible. Bone cements therefore can be used only for fixation

of endoprostheses at temperatures less than their glass transition temperature in the glassy state. The glass transition temperatures of acrylic bone cements in a dry state range from 80°–100°C. These are high temperatures compared with the temperature of the human body. The water absorption of the cement, however, results in a reduction in glass transition temperature of approximately 20°–30°C after 8 weeks of incubation in water. The glass transition temperatures of water-saturated bone cements are approximately 60°–70°C. The addition of antibiotics does not lower the glass transition significantly. Considering the pronounced difference between the glass transition temperature and the temperature of the human body, the risk for sinking of the implant caused by creep seems to be very low.[16]

Property	Value range (MPa)
Ultimate tensile strength	36 to 47
Ultimate compressive strength	80 to 94
Bending strength (4 point configuration)	67 to 72
Shear strength	50 to 69
Mean fracture toughness (K_{ic})**	1.52 to 2.02 (MPa√m)

*Simplex P, Palacos R, CMW1

**K_{ic}, mean fracture toughness of brittle materials

Table 2. Mechanical properties of three cement brands*

7.3. Creep behavior

Polymers such as PMMA bone cements exhibit a combination of elastic and viscous behavior called viscoelasticity. When a polymer is subjected to a constant load, the resulting deformation can be divided into two parts: the immediate elastic deformation and the time-dependent, continuous deformation. The immediate elastic deformation happens instantaneously by applying load. It is a recoverable deformation essentially independent of time. Following this rapid deformation there is a delayed continuous deformation resulting from stress. One part of this deformation is recoverable in time after releasing load. This part is called delayed elastic deformation or primary creep. The second part of this continuous deformation is a non-recoverable permanent deformation called secondary creep.[21]

Different test methods are described in the standard ASTM D 2990 to measure creep. The specimen is loaded by tensile, compressive, or flexural stress. In each method the change in length of the specimen is measured and divided by the original length for the calculation of creep. All plastic materials including acrylic bone cement creep to a certain extent. The degree of creep depends on several factors, such as composition of the material, temperature, load, and load duration. Delayed injection time of acrylic bone cement increased creep compared with bone cement prepared according to standard injection procedures. Creep therefore depends not only on the material properties, but also on the cement handling by the surgeon.[22] It has been proposed that creep of acrylic bone cement may contribute to loos-

ening of cemented total joint replacements. The long-term prosthetic subsidence rates caused by creep of acrylic cement, however, are small. On the other hand, cement creep relaxes cement stresses and creates a more favorable stress distribution at the interfaces. [3, 16]

7.4. Fatigue behavior

To ensure survival of the cement in the human body, the bone cement must be able to withstand the varying loads it endures. The fatigue properties of the cement thus are of particular significance, and they may determine when a correctly used cement will fail or not. Many studies have dealt with this topic, measuring fatigue properties in different ways. Today three different standard testing procedures are used to characterize the fatigue behavior:

- Four-point bending arrangement recommended by ISO 5833 standard

- Uniaxial pure tensile test with flat tapered specimens according to ISO 527

- Uniaxial compression–tension test with cylindrical tapered specimens according to ASTM F2118

- The first method is equivalent to the bending test method according to ISO 5833.

7.5. Fatigue testing

Fatigue testing is a dynamic test and is executed with a sinusoidal cyclic loading under stress control. The tests are continued until failure or until run-out. The run-out limit is a predetermined number of cycles at which the testing on a specimen is stopped, eg, 5 million or 10 million cycles. The second method is equivalent to tensile testing according to ISO 527. Again, the test run is performed with a sinusoidal cyclic loading under stress control until failure or until run-out. The third method is according to ASTM F2118. The specimens are subjected to fully reversed compressive and tensile loading in a sinusoidal cyclic manner. Again, the tests are continued until failure or until the run-out limit is reached. Most fatigue tests run at a specified frequency, eg, 5 Hz, in buffered saline solutions at 37°C.[16]

For tension–compression, the preliminary results exhibit a steeper decrease that might be caused by a possibly stronger deterioration from the additional compressive loading. The materials behave in a similar way under bending and uniaxial tension. The simplest test configuration is the standardized four-point bending test according to ISO 5833. Additionally the preparation of the specimens for the tension–compression is much more complex than the preparation of specimens for the bending test. For these two reasons the four-point bending is the preferred method for fatigue testing. The environmental conditions in which these experiments are conducted have a considerable influence on the fatigue life. Bone cements have different fatigue behavior if tested dry or in aqueous solution. The tests in air at room temperature result in a stress-number of cycles-curve (S-N-curve) of considerably higher slope. To simulate the body environment, tests should be performed in an appropriate liquid, such as simulated body fluid or Ringer's solution. The results of tests in air at laboratory temperature should be rated carefully.

Furthermore, the sterilization process of the polymer powder has an influence on fatigue be‐ havior of acrylic bone cements. Sterilization by γ-irradiation or b-irradiation significantly lowers the molecular weight of the polymer powder and the resulting cured bone cement, whereas sterilization by ethylene oxide has no influence on the molecular weight of the pol‐ ymer. Bone cement with high molecular weight has a better fatigue performance than a ce‐ ment with low molecular weight.[17]

Porosity is a major cause of reduced fatigue life of bone cement. Pores or other inclusions serve to concentrate stress in the material and often initiate fatigue cracks within the bone cement. These cracks ultimately lead to failure. The sources of porosity are air initially sur‐ rounding the powder, which is trapped during wetting of the powder, air trapping in the cement during mixing, and air trapping in the cement during transfer from mixing container to application device. Hand-mixed bone cement in an open bowl has a significantly higher number of pores than bone cement mixed in a vacuum mixing system. Modern cement mix‐ ing systems reduce cement porosity and enhance cement strength by eliminating the chan‐ ces of air entrapment in the cement.[23]

8. Antibiotics

Buchholz and Engelbrecht were the first to add gentamicin antibiotic to a bone cement.[3] Initially the antibiotic was added by hand, and subsequently during manufacture, making antibiotic-loaded acrylic cement widely available as part of antimicrobial prophylaxis in pri‐ mary arthroplasty. It was shown later, that oxacillin, cefazolin, and gentamicin are all stable in PMMA bone cement and were released in active form. The largest release of antibiotics occurred in the first 24 hours, but high bactericidal concentrations of the antibiotics were measured in the periprosthetic bone for up to 21 days after implantation. A small amount of antibiotic elution is observed even after 5 years. Bone cement without any antibiotics had no bacteriostatic effect on *Staphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa* or‐ ganisms. [24]

Bone cements can function as a matrix for the local application of antibiotics. Because of the high local concentration of an antibiotic in the surroundings of the implant, the use of bone cements has great advantages compared with a systemic antibiotic therapy. The artificial im‐ plant is especially sensitive to bacterial contamination on its surface, because the microor‐ ganisms may proliferate there almost unhampered by the immune defense of the body. As the bacteria rapidly generate a protective mucus layer and go to an inactive state with low sensitivity to antibiotics, a local antibiotic treatment is important. The pharmacokinetics of the antibiotic release from the matrix is of clinical importance. The local antibiotic concentra‐ tions reached must be clearly greater than the minimal inhibitory concentration and the minimal bactericidal concentration for the organisms. Not all antibiotics are suitable for use in bone cements. To avoid the development of resistant strains, a high initial level with a subsequent controlled release for days or weeks is important. The following bacteriologic and physical and chemical factors should be considered in the choice of an antibiotic:

1. Broad antibacterial spectra, including gram-positive and gram-negative organisms

2. Good bactericidal effect in low concentrations

3. Low incidence of primary resistant germs

4. Low rate of development of resistances

5. Low protein bonding

6. Low allergic potential

7. Little effect on bone cement mechanics

8. Chemical and thermal stability

9. Good solubility in water

10. Good release from bone cement

Based on these requirements and release tests, gentamicin has become the favorite antibiotic for bone cements since the early 1970s. Gentamicin is the most common additive because it has, amongst other features, a good spectrum of concentration-dependent bactericidal activity, thermal stability and high water solubility. [7]

Antibiotics are added in the form of powder, which is unable to diffuse through a hard, glassy polymer. So the mechanism of elution of the antibiotics is believed to be closely related to water-absorbing properties of the cement with respect to time and distance from the surface of the cement. The diffusion rate of the antibiotics depends on several factors, such as the chemical composition of the cement, the surface area at the cement-bone interface, and cement handling. For example, Palacos cement containing prepolymerized beads of P(MMA-co-MA) were shown to elute gentamicin at more rapidly than Simplex containing prepolymerized beads of P(MMA-co-S). In addition, vacuum mixing, which decreases the porosity in bone cement, can also alter the kinetics of the elution of antibiotics and was shown to decrease their rate of elution by 50%.[25]

Penner et al investigated the release of vancomycin and tobramycin from bone cement separately or combined in nonvacuum preparations. They observed that the combined use of the 2 antibiotics led to an increased elution of both from cement. Baleani et al also showed that the presence of meropenem broadened the antibacterial spectrum and enhanced the elution of vancomycin from cement. [26]

Since powder gentamicin is a costly antibiotic and is not available for hand-mixing with bone cement in operating rooms, many researchers have tried to add liquid gentamicin to bone cements. The liquid gentamicin, a much less costly antibiotic (1/20 the price of tobramycin) with a broad antimicrobial spectrum, is widely available throughout the world, but there is always a fear of deteriorating the mechanical properties of the bone cement by adding liquid gentamicin. Hsieh PH et al investigated the use of liquid gentamicin, alone and in combination with vancomycin, incorporated into acrylic bone cement as a potential treatment of complex orthopedic infections. They assessed the cement specimens loaded with

480 mg of liquid gentamicin, 4 g of powdered vancomycin, or both antibiotics for elution characteristics, bioactivity, compressive strength, and porosity. Vancomycin elution was enhanced by 146% with the addition of gentamicin liquid, and gentamicin elution was enhanced by 45% when combined with vancomycin. Bioassay confirmed the bactericidal activity of the released antibiotics. Adding liquid gentamicin increased porosity, whereas adding vancomycin did not. Compressive strength decreased by 13%, 37%, and 45% in specimens containing vancomycin, liquid gentamicin, and both antibiotics, respectively.(Table 3) Despite inferior mechanical properties, the temporary nature of cement beads and spacers makes the liquid gentamicin–vancomycin mixture a potentially more cost-effective regimen in bone cement to treat musculoskeletal infections. [27]

	Vancomycin	Gentamicin	Both antibiotics
Porosity* (%)	5.8 ± 2.6	16.8 ± 1.9	22.4 ± 3.4
Compressive strength (MPa)	79.69 ± 6.2	57.99 ± 1.5	50.32 ± 4.9

*Porosity as a percentage of the total area.

Table 3. Porosity and ultimate compressive strength of the specimens

Other antibiotics with suitable spectra against orthopaedic infecting organisms, such as cefazolin, ciprofloxacin, linezolid, levofloxacin and rifampin, have been tested according to their elution and bactericidal activities and have been shown that all these antibiotics may be suitable for incorporation into polymethylmethacrylate for management of orthopaedic infections.[28] (Table 4)

But it worth noting that all antibiotics are not suitable for adding to bone cements. Goss et al have shown that amphotericin B does not elute from polymethylmethacrylate bone cement. However, addition of this antifungal increases the mechanical strength by forming covalent crosslinks in the PMMA matrix, imparting better mechanical properties. [29]

Antibiotics premixed into the cement by the manufacturer can be advantageous since the addition of antibiotic powder manually can lead to agglomeration and a decrease in the mechanical strength of the cement. Antibiotics are added to cement in the powdered form since it was demonstrated that the addition of liquid antibiotics resulted in a decrease in mechanical strength due to interference with the early stages of polymerization of the MMA monomer. The amount of antibiotic powder required for a therapeutic level of elution is approximately 0.5 to 2 g in a standard 40-g package of prepolymerized PMMA powder. Note that antibiotic powder, like radiopacifiers and pores, also results in defects or flaws in bone cement. The flexural strength of antibiotic-containing cement was shown to be lower than that of cement without antibiotics, and the toughness of antibiotic-containing cement decreased further with excessive amounts of antibiotics. A likely reason for this is that excess amounts of undissolved antibiotics agglomerate into aggregates exceeding the critical flaw size for PMMA. However, doses of 2 g of well-dispersed antibiotic powder may not

have any adverse effect on the mechanical properties of bone cement if the size of the inclusions remains below the critical flaw size for PMMA.

Antimicrobial	Amount (%)	AUC (μg/mL/h)	Peak concentration (μg/mL)	Time no longer detectable (h)	Percent in the bead before elution
Cefazolin	2.5	18 ± 3	15 ± 2	2 ± 0	56 ± 2
	7.5	162 ± 33	62 ± 23	10 ± 1	42 ± 4
	15	792 ± 47	147 ± 22	26 ± 1	54 ± 5
Ciprofloxacin	2.5	23 ± 5	5 ± 0	45 ± 3	36 ± 3
	7.5	112 ± 3	15 ± 1	45 ± 5	36 ± 7
	15	307 ± 10	54 ± 3	48 ± 0	31 ± 3
Gatifloxacin	2.5	157 ± 34	15 ± 2	48 ± 0	45 ± 2
	7.5	190 ± 65	19 ± 1	48 ± 0	47 ± 4
	15	499 ± 51	51 ± 3	48 ± 0	50 ± 3
Levofloxacin	2.5	33 ± 4	7 ± 1	48 ± 0	28 ± 3
	7.5	123 ± 7	26 ± 3	48 ± 0	23 ± 3
	15	291 ± 59	52 ± 10	48 ± 0	24 ± 3
Linezolid	2.5	Not detected	<5	0 ± 0	96 ± 5
	7.5	213 ± 53	43 ± 4	12 ± 4	88 ±4
	15	224 ± 155	64 ± 47	22 ± 2	84 ± 4
Rifampin	2.5	5 ± 2	4 ± 1	2 ± 1	21 ± 1
	7.5	147 ± 15	15 ± 2	37 ± 1	27 ± 4
	15	409 ± 46	31 ± 11	48 ± 0	24 ±1

AUC: area under the curve

Table 4. Parameters of release from PMMA for studied antimicrobials

8.1. Costs of antibiotic-loaded bone cement

Currently the increased acquisition cost of commercially available antibiotic-loaded bone-cement products is considerable. Compared with the cost of plain bone-cement products, the cost of equivalent antibiotic-loaded bone-cement products is increased anywhere from $284 to $349 (United States dollars) per 40-g packet. If the historical 11% usage of antibiotic-loaded bone cement increased to 50% of the estimated 500,000 primary total joint arthroplasties performed annually in the United States, and if two packets of cement (at a $300 increased cost per packet) were used for each joint replacement, the increase in overall health-care costs would be $117,000,000 for the 195,000 additional cases. This estimated increased

health-care cost must be balanced with the potential cost savings associated with a realized reduction in the rate of infection associated with routine use of antibiotic-loaded bone cement for prophylaxis in primary total joint replacement. At an approximately $50,000 cost for the treatment of an infection at the site of a total joint replacement, there would have to be 2340 fewer infected patients among the additional 195,000 patients for the routine use of antibiotic-loaded bone cement to be fiscally neutral. With a rather high estimated infection rate of 1.5%, a deep postoperative infection could be expected to develop in 2925 of 195,000 patients. In other words, the rate of deep periprosthetic infection would need to be reduced from this 1.5% to 0.3% to recover the costs associated with the routine use of commercially available low-dose antibiotic-loaded bone cement in primary total joint arthroplasty. Moreover, while the estimated costs for the treatment of an infection at the site of a total joint arthroplasty do not account for morbidity and mortality associated with the treatment required, the increased costs associated with the treatment of more drug-resistant organisms are unknown. [30]

8.2. Choice of antibiotic in antibiotic-loaded bone cement used prophylactically

The aminoglycoside antibiotics were originally selected for use in antibiotic-loaded bone cement because of their broad bacterial coverage and their low allergy profile. Because the level of gentamicin or tobramycin in the joint is often ten times greater than safe blood levels, the efficacy of those drugs is excellent unless the organism has a specific resistance to them. Gentamicin and tobramycin are also the only antibiotics currently available in commercially premixed low-dose antibiotic-loaded bone-cement preparations. As mentioned above, however, low doses of other types of antibiotics, including several of the cephalosporins, have been hand-mixed into bone-cement preparations, and those preparations have had good success in prophylactic applications. Allergic reactions have not been reported, to our knowledge, but it is prudent for the surgeon to consider the individual patient's allergy history before selecting the antibiotic for antibiotic-loaded bone cement. There has been considerable research on the primary bacterial contaminants in total joint surgery.

Al-Maiyah et al. took 627 blood-agar impressions of the gloved hands of surgical personnel during the performance of fifty total hip arthroplasties in England. Bacteria grew on culture of fifty-seven impressions (9%); 69% were coagulase-negative staphylococci, 12% were Micrococcus, 9% were diphtheroids, and 6% were *Staphylococcus aureus*. Of the coagulase-negative staphylococci, only 52% were sensitive to cefuroxime. In contrast, Ridgeway et al. found *Staphylococcus aureus* in 50% of the surgical site infections (both superficial and deep) in their multiple-hospital study in England. More than half of the *Staphylococcus aureus* isolates were methicillin-resistant. Thus, it appears that staphylococcal species are the primary bacteria toward which antibiotic-loaded bone cement would be directed. The currently available commercial gentamicin or tobramycin-loaded bone cements provide sufficient elution concentrations to be bactericidal even against methicillin-resistant organisms. Vancomycin may also be added to bone cement, but it has a lower efficacy than gentamicin or tobramycin at these concentrations. The use of vancomycin should be considered in revisions following primary arthroplasties in which gentamicin or tobramycin-loaded bone cement had

been used because of the prevalence of gentamicin resistance in association with such revisions. Cephalosporins may also be considered for antibiotic-loaded bone cement that is to be used prophylactically but may not be effective against methicillin-resistant organisms.[30]

9. Adverse effects of bone cement

9.1. Cardiopulmonary complications

Cardiopulmonary complications associated with PMMA have been reported in conjunction with hip arthroplasty and VA. Prior studies have postulated that PMMA-associated hypoxia, hypotension, and death may occur as a result of the toxic effects of monomer or anaphylaxis. Other literature indicates that the application of PMMA may lead to embolization of marrow debris and neurogenic reflex, thus adversely affecting cardiopulmonary function. Pulmonary infarction and death have been reported as a result of embolization of PMMA that was injected in liquid state following VA. [2]

9.2. Hypersensitivity to components of methylmethacrylate, especially benzoyl peroxide

A small but significant proportion of cemented total knee arthroplasties develop early aseptic loosening. Polyethylene debris is unlikely to be the cause in the small subgroup that experiences early loosening. Allergy to polymethylmethacrylate bone cement or its constituents has been reported in dentistry, dermatology, and joint arthroplasty. Although allergy to polymethylmethacrylate bone cement or its constituents is unusual, the possibility of a systemic inflammatory response and consequent pain and loosening must be considered. Benzoyl peroxide is an essential component of bone cement. Direct evidence for allergic reactions to benzoyl peroxide has been reported in dental and dermatological literature. The currently accepted model for this delayed hypersensitivity is that a hapten such as benzoyl peroxide conjugates with a body protein, which creates a neoantigen capable of stimulating an immune response. This hypersensitivity places the patient at risk of developing insidious pain, a systemic inflammatory response, and possibly aseptic loosening. After revision to uncemented femoral and tibial components, the patient's symptoms vastly improved.[31]

9.3. Presence of components of methylmethacrylate in serum and breast milk

Singh et al. reported dose-related teratogenic and fetal toxic effects of methacrylic acid administered via the intraperitoneal route in rats. McLaughlin et al. exposed pregnant mice to very high vapor concentrations of methacrylic acid of 1330 parts per million for two consecutive hours, twice daily. The mice demonstrated no evidence of fetal toxicity or teratogenic effects; in fact, there was a slight increase in fetal weight with methacrylic acid exposure. The only published study that has addressed methacrylic acid exposure during lactation involved a patient undergoing arthroplasty, not operating room personnel who were exposed to methacrylic acid vapors. In that study, Hersh et al. found undetectable levels of polyme-

thylmethacrylate in breast milk that was collected thirty-six hours after hybrid total hip arthroplasty in a twenty-nine-year-old woman who was five months postpartum. Linehan et al. showed undetectable levels of methacrylic acid (at the 0.5-part-per-million level) in the serum and breast milk of two lactating surgeons who had been exposed to typical operating room conditions without the use of personal exhaust systems. [32]

10. Composite bone cements

PMMA-based bone cement has a high modulus but low toughness compared with ductile polymers. In order to address the lack of fracture toughness and fatigue strength, many investigators who have developed new composite PMMA cements use the concept of fiber reinforcement and incorporate a low-volume fraction of chopped fibers of approximately 1% to 2%.[33] Several types of fibers, such as fibers made of carbon, polyethylene terephthalate, oriented PMMA, ultra high molecular weight polyethylene, titanium, aramid, Kevlar, graphite, steel, and zirconia fibers with and without acrylic coating have been used to reinforce PMMA-based bone cement.[33-6] While these composites have displayed improved fatigue failure properties, biocompatibility concerns and complications of processing have prevented their implementation in the manufacture of PMMA bone cement.

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