PREPARATION AND CHARACTERIZATION OF ACRYLIC BONE CEMENTS

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ABSTRACT

PREPARATION AND CHARACTERIZATION OF ACRYLIC BONE CEMENTS

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Acrylic bone cements are used in dentistry and orthopedic surgery to fix prosthetic devices into the bone. Bone cements transfer and distribute the applied load and increase the load-carrying capacity of the prosthesis/cement/bone system with the help of mechanical bonding between the device and the bone. In spite of all their advantages, bone cements have several drawbacks such as insufficient mechanical properties, high exothermic polymerization temperature, release of monomer to the environmental tissue and loosening of implant. Studies are being carried out to improve bone cement formulations with low curing temperature, good mechanical properties and good biocompatibility. In this study, bone cements with different compositions were prepared by using poly(methyl methacrylate) (PMMA) microspheres, barium sulphate ($BaSO_4$) radiopaque agent, inorganic hydroxyapatite (HA) particles and 1-dodecyl mercaptan (DDM) chain stopping agent. Mechanical and thermal properties of the prepared bone cements were examined. When 8% hydroxyapatite was added into the formulation, both tensile and compressive strengths were increased and curing temperature was decreased. Addition of 13% $BaSO_4$ caused 0.98% and 10.29% decrease in tensile and compressive strength values, respectively. Addition of 1%, 2% and 3% DDM, relative to the amount of methyl methacrylate monomer, decreased the

maximum temperature from 101.78°C to 91.80°C, 78.38°C and 71.35°C, respectively.

All compositions of the prepared bone cements fulfilled the minimum compressive strength (70 MPa) requirement and the minimum curing temperature was obtained as 71.35°C. In order to have optimum desired properties, further studies to improve biocompatibility, mechanical and thermal properties of bone cements are needed.

Keywords: Bone cement, acrylic cement, poly(methyl methacrylate), microsphere, hydroxyapatite.

ÖZ

AKRİLİK KEMİK ÇİMENTOLARININ HAZIRLANMASI VE KARAKTERİZASYONU

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Tez Yöneticisi: Prof. Dr. Nesrin HASIRCI

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Akrilik kemik çimentoları protezi kemiğe sabitlemek amacıyla diş hekimliği ve ortopedik cerrahide kullanılmaktadır. Kemik çimentoları; uygulanan yükleri implanttan kemiğe transfer eder ve implant ve kemik arasındaki mekanik bağ yardımıyla implant/çimento/kemik sisteminin yük taşıma kapasitesini arttırır. Kemik çimentolarının pek çok avantajlarının yanı sıra; düşük mekanik özellikler, yüksek ekzotermik polimerizasyon sıcaklığı, çevre dokuya monomer salımı ve aseptik gevşeme gibi bazı dezavantajları da vardır. Düşük kür sıcaklığına, iyi mekanik özelliklere sahip ve biyouyumlu bir kemik çimentosu geliştirmek için çalışmalar yürütülmektedir. Bu çalışmada, poli(metil metakrilat) (PMMA) mikroküreleri, baryum sülfat ($BaSO_4$) radyoopak madde, inorganik hidroksiapatit (HA) partikülleri ve 1-dodecil merkaptan (DDM) zincir durdurucu kullanılarak değişik kompozisyonlara sahip kemik çimentoları hazırlanmıştır. Hazırlanan çimentoların mekanik ve termal özellikleri incelenmiştir. Kompozisyona %8 hidroksiapatit eklendiğinde çekme ve basma dayanımı artmış ve kür sıcaklığı azalmıştır. %13 $BaSO_4$ eklenmesi çekme ve basma dayanımında sırasıyla %0.98'lik ve %10.29'luk düşüşe neden olmuştur. Metil metakrilat monomer miktarının %1, %2 ve %3'ü kadar DDM eklenmesi kür sıcaklığını 101.78°C'den sırasıyla 91.80°C, 78.38°C ve 71.35°C'ye düşürmüştür.

Hazırlanan kemik çimentolarının hepsi minimum basma dayanımı şartını (70 MPa) karşılamıştır ve minimum kür sıcaklığı 71.35°C olarak gözlemlenmiştir. Kemik çimentolarının istenilen optimum özelliklerde olabilmesi için biyouyumluluğunu, mekanik ve termal özelliklerini geliştirmek yönünde daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Kemik çimentosu, akrilik çimento, poli(metil metakrilat), mikroküre, hidroksiapatit.

To My Dear Family,

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ANP	Acryloyl-N-phenylpiperazine
$BaSO_4$	Barium sulphate
BC	Bone cement
BPO	Benzoyl peroxide
C-Cr-Mo	Carbon–Chromium–Molybdenum
CF	Carbon fiber
DDM	1-Dodecyl mercaptan
DEABM	4-diethyaminobenzyl methacrylate
DEAEM	Diethyl amino ethyl methacrylate
DHPPT	Dihyroxypropyl-p-toluidine
DMA	n-decyl methacrylate
DMOH	4-N,N-dimethylamino benzyl alcohol
DMPT	N,N-dimethyl-p-toluidine
E_C	Compressive modulus of elasticity
E_T	Tensile modulus of elasticity
EGDMA	Ethylene glycol dimethacrylate
EtO	Ethylene oxide
FTIR	Fourier Transform Infrared Spectrometer
HA	Hydroxyapatite
HQ	Hydroquinone
IBMA	Isobornyl methacrylate
IEMA	2-[4-iodobenzoyl]-oxo-ethylmethacrylate
IHQM	2,5-diiodo-8-quinolyl methacrylate
κ	Thermal conductivity
KBr	Potassium bromide
MAA	Methacrylic acid
MBA	4-methacryloyloxybenzoic acid
META	4-methacryloyloxyethyl trimellitate
MMA	Methyl methacrylate
MNP	Methacryloyl-N-phenylpiperazine

MVE	Vitamin E
NaOH	Sodium hydroxide
NMR	Nuclear Magnetic Resonance Spectrometer
PA	Poly(acetal)
PE	Poly(ethylene)
PEEK	Poly(etherether ketone)
PEG	Poly(ethylene glycol)
PET	Poly(ethylene terepthalate)
PGA	Poly(glycolic acid)
PLA	Poly(lactic acid)
PMMA	Poly(methyl methacrylate)
PP	Poly(propylene)
PS	Poly(sulfone)
PTFE	Poly(tetrafluoroethylene)
PU	Poly(urethane)
PVA	Poly(vinyl alcohol)
SBF	simulated body fluid
SEM	Scanning Electron Microscopy
SR	Silicone rubber
TBB	tri-n-butylborane
TCP	β-Tricalcium phosphate
TEG	Ethoxytriethyleneglycol methacrylate
T_g	Glass transition temperature
Ti-Al-V	Titanium–Aluminum–Vanadium
UCS	Ultimate compressive strength
UHMWPE	Ultra high molecular weight polyethylene
UTS	Ultimate tensile strength
ZrO_2	Zirconium dioxide

CHAPTER 1

INTRODUCTION

1.1 Biomaterial

Biomaterial is defined as the material used to replace part of a living system which is not functioning properly or to help the biological system in intimate contact with living tissue. Biomaterials can be in the forms of medical devices such as pacemakers, biosensors, artificial hearts, blood tubes or implants placed in the body such as sutures, bone plates, joint replacements, ligaments, vascular grafts, heart valves, intraocular lenses, dental implants etc. Certain metal alloys, polymers, ceramics and composites are used as biomaterials in the design and production of biomedical devices [1].

Metals are tough and ductile materials; they have good mechanical strength and low corrosion resistance and generally used for load bearing applications such as prosthesis, pins, nails, rods and plates. Low carbon stainless steel, alloys of Ti-Al-V (Titanium–Aluminum-Vanadium) and C-Cr-Mo (Carbon–Chromium–Molybdenum) are some examples for metallic biomaterials [2].

Polymers have lower mechanical properties than metals but they have very wide versatility. In orthopedic area, poly(ethylene) (PE) is used in artificial acetabular cup and poly(methyl methacrylate) (PMMA) is used in bone cement production. In addition; polymers such as poly(urethane) (PU), poly(tetrafluoroethylene) (PTFE), poly(acetal) (PA), poly(ethylene terepthalate) (PET), silicone rubber (SR), poly(sulfone) (PS), poly(etherether ketone) (PEEK), poly(lactic acid) (PLA), and poly(glycolic acid) (PGA) are also used in various biomedical applications [3].

Ceramics are used as coating material or in non-load bearing applications. Calcium phosphates, zirconia and alumina are examples of bioceramics. They have good tissue response and are typically strong but brittle in nature [2].

Therefore, polymer-ceramic compositions are preferred to increase the mechanical properties of both ceramics and polymers. Hydroxyapatite/poly(ethylene) (HA/PE), silica/silicone rubber, carbon fiber/ultra high molecular weight polyethylene (CF/UHMWPE), carbon fiber/epoxy (CF/epoxy), and CF/PEEK are few examples of polymer-ceramic composite biomaterials. Composites are multiphase materials and demonstrate significant proportion of properties of each phase [3].

Materials which will be used as an implant must fulfill some requirements; first of all they must be biocompatible. Biocompatibility is defined as the acceptance of an artificial implant by the surrounding tissues and by the body as a whole [1]. An appropriate biomaterial must be nontoxic, non-carcinogenic, chemically inert, stable and mechanically strong enough to withstand the repeated forces of a lifetime of use.

Biomaterials have wide application areas; they are used in orthopedic, dental and cardiovascular applications, cosmetic surgery as well as supporting materials in hospitals. Bone cements, replacement parts of bones and joints, dental adhesives, heart prosthetics, heart replacement valves, artificial lungs and kidneys can be given as some examples of biomaterials and they improve the quality of life of patients [4]. One of the most common applications of biomaterials is in orthopedic area as implant devices used in total joint replacement.

1.2 Total Joint Replacement

Joints provide the movement of the body and its parts. Therefore, it become possible to do various physical activities such as walk, jog, run, jump, turn, bend, bow, stand, and sit in daily life. Most of the joints in the body are synovial types, which permit free movement. Hip, knee, shoulder, and elbow are a few common examples of synovial joints [3]. During daily activities bones are subjected to a stress of approximately 4 MPa whereas the tendons and ligaments experience peak stresses in the range 40–80 MPa. The mean load on a hip joint is up to 3 times of body weight and peak load during jumping can be as high as 10 times of body weight [5].

Total joint replacement is the renewal of the damaged or diseased part of the joint with a plastic or metal device called prosthesis. The most common total joint replacements are hip and knee replacements furthermore other joints such as the ankle, foot, shoulder, elbow and fingers may also need replacement in case of injury. Osteoarthritis, rheumatoid arthritis, traumatic arthritis and avascular necrosis (osteonecrosis) are main reasons that cause total joint replacement.

- Osteoarthritis is a specific form of degenerative arthritis caused by wear and tear from overuse or from aging and therefore it allows the bones touch each other.
- Rheumatoid arthritis is a chronic, autoimmune disease causing inflammation of the joint lining called the synovial membrane, and destruction and deformity of bone, cartilage, ligament and muscle tissue.
- Traumatic arthritis is a type of arthritis resulting from a hip injury that can cause debilitating pain leading to replacement of the hip. The articular cartilage can tear and cause increased friction and accelerated degeneration of the joint.
- Avascular necrosis is the result of a loss of blood supply to the ball or head of the femur bone. As a result, articular cartilage wears away leaving a "bone on bone" interaction for hip joint movement [6].

In an arthritic knee the damaged ends of the bones and cartilage are replaced with metal and plastic surfaces that are shaped to provide knee movement and function. In an arthritic hip, the damaged ball (the upper end of the femur) is replaced by a metal ball attached to a metal stem fitted into the femur, and a plastic socket is implanted into the pelvis, replacing the damaged socket. The prosthesis contains a metal piece that fits closely into a matching sturdy plastic piece. Several metals such as stainless steel, alloys of cobalt and chrome, and titanium are used. The plastic material, which commonly used is poly(ethylene), and it is durable and resistant to wear [6]. Typical hip and knee implants are shown in Figure 1.1.

There are two methods for fixation of implant, which are mechanical interlock and biological fixation. Mechanical interlock is supplied by press-fitting the implant by using PMMA bone cements as a grouting agent. Biological fixation is achieved by using textured or porous surfaces therefore bone can grow into the

interstices and direct chemical bonding between implant and bone is achieved by coating the implant with calcium hydroxyapatite, which has a mineral composition similar to bone, and its clinical application is still under investigation. Fixation of implants with PMMA bone cement provides immediate stability and therefore allows patients to carry all of their body weight in a short time. In contrast, implants, which depend on bone ingrowth, require the patient to wait about 12 weeks to carry all of their weight [4].

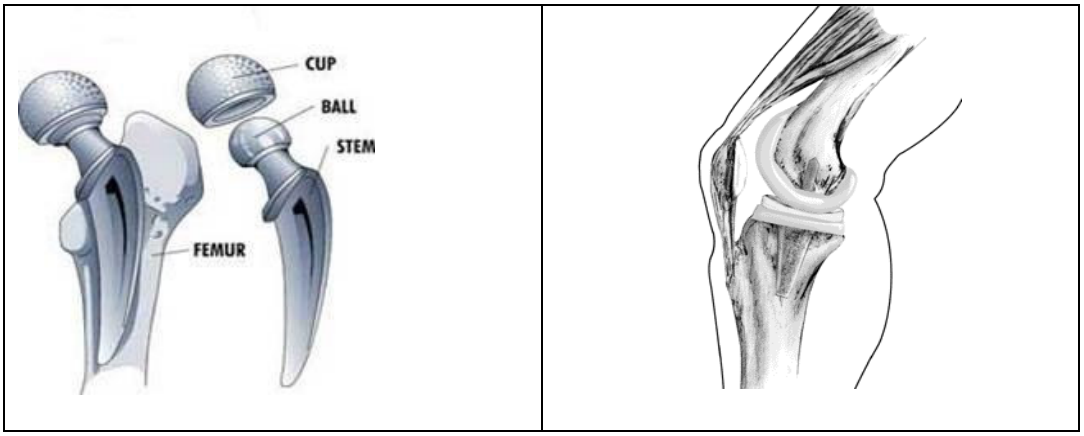

Figure 1.1 Hip and knee implants [7]

1.3 Bone Cements

Bone cements are used in dentistry and orthopedic surgeries to fill cavities, to replace or bind bone fragments resulting from trauma or to fix implanted prosthesis into the required places of the bone [2]. They transfer and distribute the applied load and increase the load-carrying capacity of the prosthesis-cement-bone system with the help of mechanical bonding between the device and the bone [8]. Bone cements do not have adhesive properties; therefore can not be counted as glue.

PMMA polymeric plates were first used in a medical application to cover skull defects in the late 1930's [1] while PMMA bone cements were first introduced by Dr. John Charnley, an English orthopedic surgeon, in the early 1960's in the total hip replacement [4]. Bone cements are used in over 80% of hip and over 90% of knee replacements [7]. PMMA matches with the shape of its surrounding and

provides even distribution of load caused by the implant; this property of PMMA forms a strong mechanical bond with the implant [9].

PMMA is a biocompatible polymer and its manipulation is easy, due to these properties it is also used in the design of biomedical devices like blood pumps and reservoirs, membranes for blood dialyzers, in vitro diagnostics, implantable ocular lenses and contact lenses, etc. [10].

1.4 Compositions of Acrylic Bone Cements

All commercially available acrylic cements are based on mixing of a liquid component and a powder component. The composition of powder and liquid parts may have some variations but usually the powder part consists of PMMA polymer or PMMA based copolymers, benzoyl peroxide (BPO) initiator and barium sulphate ($BaSO_4$) or zirconium dioxide (ZrO_2) radiopacifiers. The chemical structures of PMMA and BPO are shown in Figure 1.2. The liquid part includes methyl methacrylate (MMA) monomer, N,N-dimethyl-p-toluidine (DMPT) as an accelerator to initiate the polymerization of MMA at room temperature and hydroquinone (HQ) inhibitor to prevent premature polymerization when exposed to light or heat. In addition; liquid part may contain a cross-linking agent such as ethylene glycol dimethacrylate (EGDMA). The chemical structures of MMA, DMPT and hydroquinone are shown in Figure 1.3. All these chemicals should be added in certain amounts as well as should have some certain ratios among each other, in order to have a proper bone cement. Composition ranges of bone cement formulations are given in Table 1.1 [11].

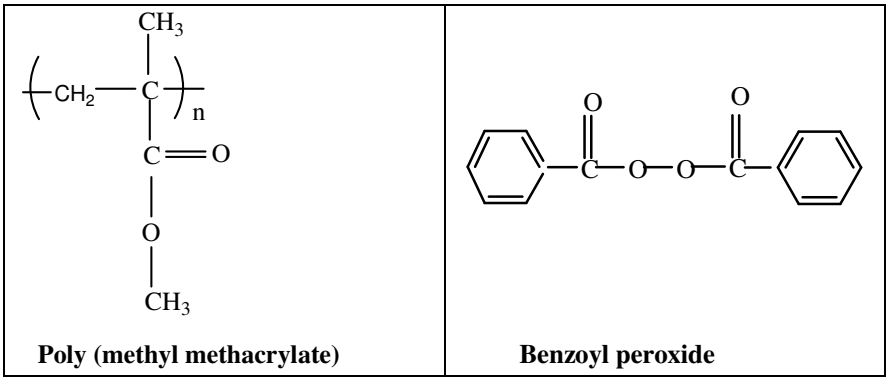

Figure 1.2 Chemical structures of powder components

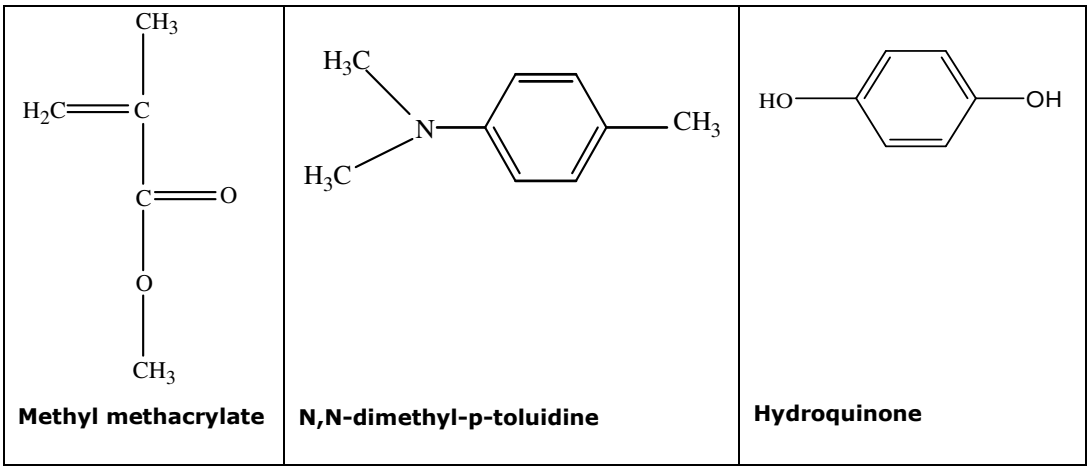

Figure 1.3 Chemical structures of liquid components

Table 1.1 Compositions of bone cements

Material	Typical Range
Powder component	
Polymer powder	84-100 wt%
Radiopaque filler	0-15 wt%
Benzoyl peroxide	0.5-2.5 wt%
Liquid component	
Methyl methacrylate	77-98 wt%
Hydroquinone	20-75 ppm
N,N-dimethyl-p-toluidine	0.7-2.5 wt%

Various types of acrylic bone cements are commercially present. They have several differences such as molecular weight, particle size and amount of polymer, presence of copolymer, type of radiopacifier, amounts of accelerator and initiator, presence of additives for example antibiotics, colourants, etc. Six different types of commercially available bone cements that are commonly used are; CMW™-1, CMW™-3 (Wright Medical Technology, Arlington, TN), Palacos® R (Smith & Nephew Orthopedics, Memphis, TN), Simplex-P (Howmedica, Inc., Rutherford, NJ), Zimmer Regular® and Zimmer Low Viscosity Cement (LVC®, Zimmer, Inc., Warsaw, TN). Their compositions are given in Table 1.2. The main differences between these six formulations are molecular weight and amounts of homopolymer, copolymer and other constituents (for example ZrO_2 is used as a

radiopacifier in Palacos® R while $BaSO_4$ is used in others and chlorophyll is present in Palacos® R as a contrast agent) [8].

Table 1.2 Compositions of six commercial bone cements

	Formulation					
Constituent	**CMW-1**	**CMW-3**	**Palacos R**	**Simplex-P**	**Zimmer Regular**	**Zimmer LCV**
Powder (weight%)						
BPO	2.6	2.2	0.5-1.6	1.19	0.75	0.75
$BaSO_4$	9.1	10	-	10	10	10
ZrO_2	-	-	14.85	-	-	-
Chlorophyll (ppm)	-	-	200	-	-	-
PMMA	88.3	87.8	-	16.55	89.25	89.25
P(MMA/MA)	-	-	83.55-84.65	-	-	-
P(MMA/ST)	-	-	-	82.26	-	-
Liquid						
N,N-DMPT	0.4	0.99	2.13	2.48	2.73	2.75
Hydroquinone (ppm)	15-20	15-20	64	75	75	75
MMA	98.66	98.07	97.87	97.51	97.27	97.25
Ethanol	0.92	0.92	-	-	-	-
Ascorbic acid	0.02	0.02	-	-	-	-
Chlorophyll (ppm)	-	-	267	-	-	-

1.5 Preparation of Bone Cement

In order to prepare bone cement; powder and liquid parts should be combined and mixed in a sterile container. After the mixing of powder and liquid parts, some physical events such as solvation of polymer and BPO in the liquid, diffusion of liquid into the organic matrix of powder part, polymer-polymer diffusion from the liquid to the solid phase and monomer evaporation from the mixture take place [12]. Usually polymer-to-monomer ratio is chosen as 2.00

(w/v) and many commercial bone cements are sold as a package of 40.0 g powder and an ampoule of 20 mL liquid. Benzoyl peroxide (BPO) in the powder component, which is the initiator and N,N-dimethyl-p-toluidine (DMPT), the accelerator, initiate the polymerization of methyl methacrylate (MMA) monomer around poly(methyl methacrylate) particles. Various mixing methods such as hand mixing, vacuum mixing and centrifugation can be applied. After the powder and liquid parts are mixed, a dough is formed and when its viscosity is high enough, the dough is placed in the implant site and then the implant is inserted while the cement is allowed to fully polymerize and solidify around the implant.

Bone cement can be placed in the implant site manually or by using a syringe or a cement gun. When a syringe or cement gun is used, it can be easier to reach into a femoral canal while the application of pressure can reduce porosity by helping penetration into the bone [13]. The polymerization is very rapid, exothermic and reaches completion in approximately 10–15 minutes, at which point the cement has set [11].

Generally; BPO initiator which exist in powder part, is not a toxic substance. It may have primary skin irritation at the 5000 mg/kg level. It is inactive on skin and not acts as a carcinogen or as a tumor initiator [14]. Also; tri-n-butylborane (TBB) may be used as initiator, and it is present in commercial bone cement Bonemite®.

DMPT is a tertiary aryl amine and commonly used in bone cement as an accelerator to activate the polymerization of MMA at room temperature. It decomposes BPO at room temperature to provide free radicals. Very limited toxicity data for DMPT have been reported in the literature [14]. Tanzi et al. tried to develop less toxic accelerator systems by using unsaturated tertiary-aryl-amines, such as acryloyl-N-phenylpiperazine (ANP) and methacryloyl-N-phenylpiperazine (MNP) instead of DMPT. It was reported that compressive yield stress, strain at yield and elastic modulus of samples cured with DMPT and ANP were similar while the results were slightly lower for samples cured with MNP [15].

The illustration of bone, bone cement and hip prosthesis in a total hip replacement is given in Figure 1.4; bone cement is placed as a thin layer between the bone and the metal stem [16].

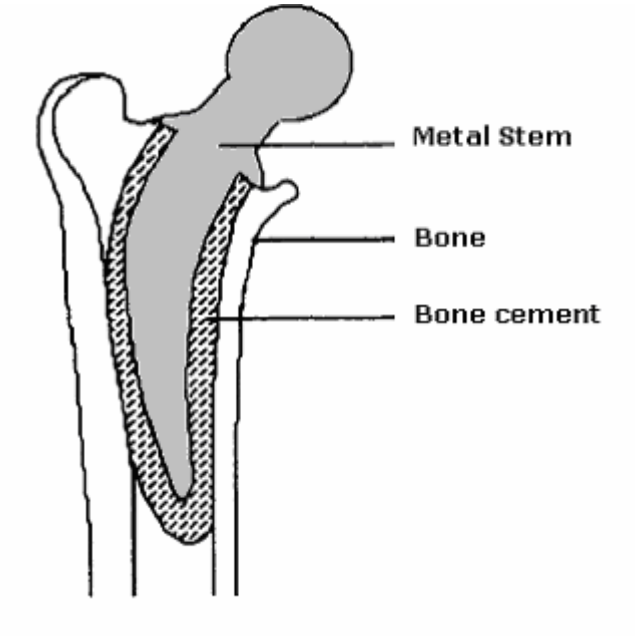

Figure 1.4 Schematic illustration of bone cement in hip joint prosthesis

1.6 Polymerization Reaction

MMA is a vinyl monomer which is polymerized by chain (free radical) polymerization reaction. Chain polymerization consists of initiation, propagation and termination stages; an initiator is required to form free radicals which then react with other units to cause chain growth. Radicals are formed as a result of reduction-oxidation reaction of BPO and DMPT. Brauer et al. suggested a mechanism for the formation of free radicals as shown in Figures 1.5-1.9 [17]. Firstly, an electron is transferred from the unshared pair of the nitrogen to the peroxide. Then benzoylate anion removes a proton from amino cation. As a result of an electron transfer from carbon to the nitrogen free radicals are formed. The amino cation is not an effective initiator and disappears by unknown side reactions (Figures 1.5 and 1.6).

Benzoyl free radical can attach itself to a MMA monomer, and then electrons in BPO/MMA compound are rearranged and create a new free radical in the monomer which can attach itself to another MMA monomer. This part is the initiation stage of polymerization and forms the initials of MMA molecule chains (Figure 1.7).

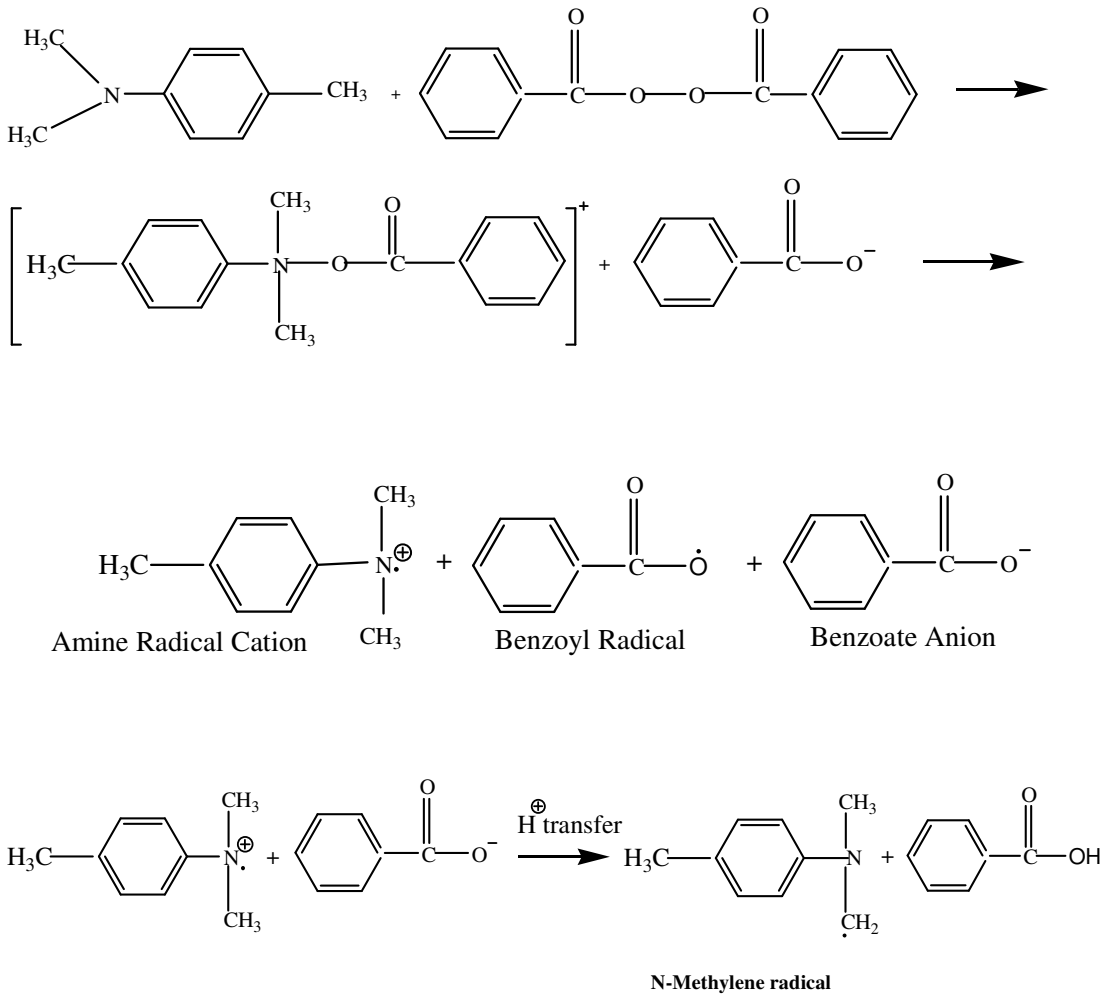

Figure 1.5 Redox reaction between BPO and DMPT

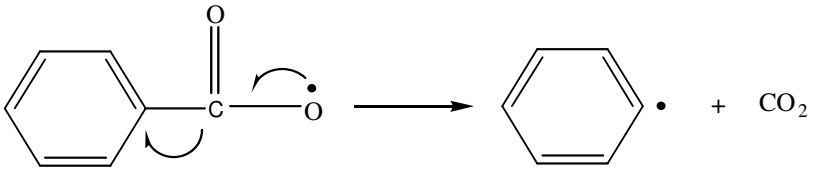

Figure 1.6 Radical formation

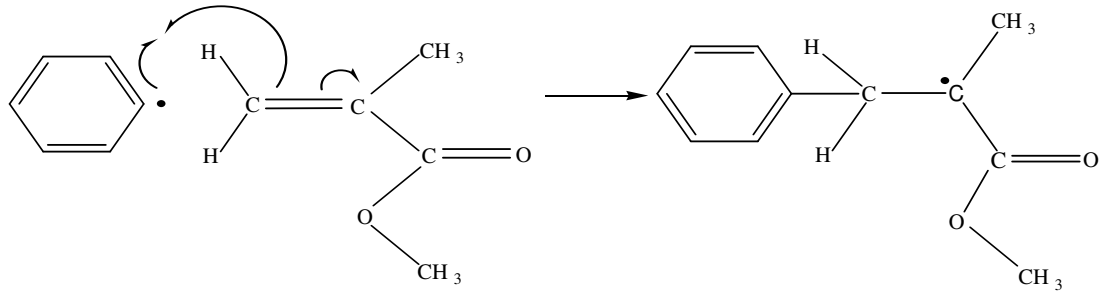

Figure 1.7 Initiation step of MMA polymerization

Second stage of polymerization is propagation, in this stage MMA monomer with its free radical react with other monomer molecules and the chain grows. Ultimately, chains with 20 to 20.000 repeating units of monomer can be formed (Figure 1.8).

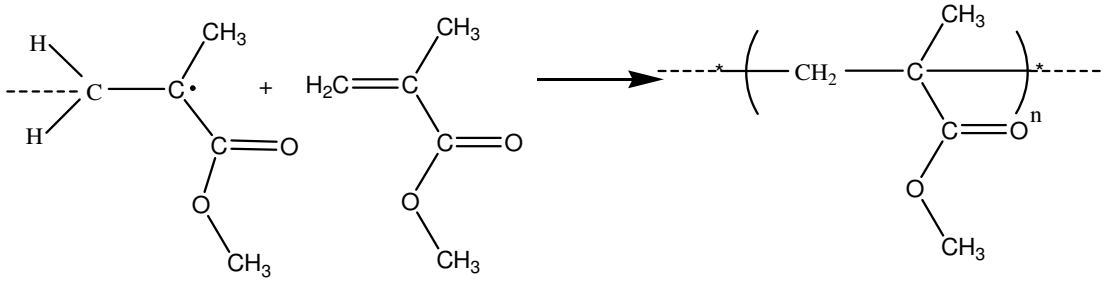

Figure 1.8 Propagation step of MMA polymerization

Third stage of polymerization is termination of chain growth. In this stage, free radical of chain terminates with the combination of free radicals or ions to form a new uncharged bond (Figure 1.9).

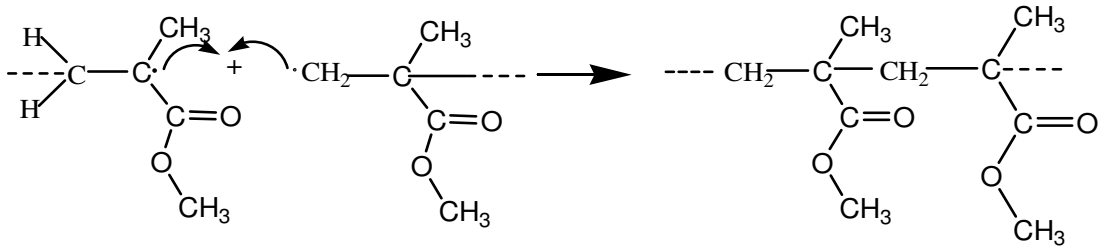

Figure 1.9 Termination step

As polymerization goes on, viscosity increases causing difficulty in diffusion and causes a decrease in termination rate leading gel effect. It is also known as auto-acceleration of the polymerization since there is a sudden increase in rate of conversion and in the molecular weight of polymer. Gel effect occurs at 20-40% conversion and it depends on the temperature and amount of initiator. The terms Trommsdorf or Norrish-Smith effect is also used for gel effect [18].

During the polymerization of MMA, carbon double bond in the MMA monomer is broken and replaced by a single bond, this process leads to release of 544 J/g of heat for each broken bond [12]. Therefore; polymerization reaction is highly exothermic and cause temperature rise. The amount of temperature rise depends on the mass, thickness of the cement, ambient temperature, and heat dissipation to the surrounding. Hansen et al. compared maximum temperatures of nine different bone cements and found a temperature range of 66-82.5ºC at the center of 6 mm samples [19]. Wang et al. showed that in vivo temperatures at the center of the cement change between 67-124ºC, depending on the cement composition [20]. In the literature it was reported that at the bone-cement interface the temperature was lower than the bulk because of thin cement mantle, the wet environment and dissipation of heat by metallic implant [21]. It was stated that temperature of 56ºC was enough to cause thermal necrosis of tissue and the extent of necrosis depends on the temperature rise and the duration which tissue is exposed to that heat [22].

1.7 Drawbacks of Bone Cement

Although acrylic bone cements have been used in orthopedic applications for prosthesis fixation and as cavity filling materials for decades, they have several drawbacks such as:

- Insufficient mechanical strength
- High exothermic polymerization temperature
- Release of monomer from cement to tissue
- Loosening of implant
- Allergy and anaphylactic reactions

Suitable bone cement should be biocompatible and not cause any allergic reaction in the body; it should also have good handling properties for the surgeon to provide easiness during application, high mechanical strength to endure cyclic loads applied during daily activities and low curing temperature in order not to give any damage to the environmental tissue.

The properties of bone cements are affected by many parameters and some of them are; composition and particle size of the powder part, composition of the liquid part, polymer-to-monomer ratio, amount of initiator and accelerator, mixing method and temperature of powder and liquid parts.

The requirements specified by the American Society for Testing and Materials (ASTM F-451) for PMMA bone cement are given in Table 1.3.

Table 1.3 Requirements for acrylic bone cement

Working time	maximum 5 minutes
Setting time	5-15 minutes
Strength	minimum 70 MPa
Solubility	maximum 0.05 mg/cm^3
Temperature rise	maximum 90ºC
Intrusion	minimum 2.0 mm

1.8 Mechanical Properties of Bone Cement

Bone cements are exposed to tensile, compressive and shear forces in the body, therefore suitable bone cement should have high mechanical strength to endure these loads applied during daily activities and it should transfer the loads homogenously from the implant to the surrounding bone. Cement breakdown and failure, limit the lifetime of bone cement and lead to revision of the implant.

The mechanical properties of PMMA may vary with temperature, environment, mixing procedure, porosity, strain rate and cement formulation. Furthermore; monomer-to-polymer ratio affects the mechanical properties of cement; as this ratio increases amount of polymer will decrease and so will the reinforcing effect of PMMA polymer. Belkoff et al. investigated the effect of monomer-to-polymer ratio on compressive properties of bone cement and observed that compressive strength increased with increasing polymer amount. It was reported that when monomer-to-polymer ratio was kept as 1:2, the compressive strength was 68.6 MPa and it decreased to 51.2 MPa when monomer-to-polymer ratio changed to 1:1 [23]. PMMA is a glassy, amorphous, thermoplastic polymer and it is known to be a low strength brittle material at body temperature. PMMA is stronger in compression than in tension and shear, and it is viscoelastic. Typical range of values of PMMA bone cement can be given as follows [2]:

- Elastic modulus 2.2-3.7 GPa
- Compressive strength 78-120 MPa
- Tensile strength 13.2-48.2 MPa

Acrylic bone cements are known to be brittle, weak in tension and have low fatigue strength. They are the weak links of bone-cement-prosthesis system. In order to improve its mechanical properties; stainless steel, titanium wires, various polymeric fibers such as poly(ethylene), carbon, Kevlar and poly(methyl methacrylate) are added to the cement [24]. However; reinforced cements have not yet been accepted in current clinical practice because addition of fibers increases the viscosity of bone cement and decreases its workability and deliverability.

1.8.1 Aseptic Loosening

The average service life of a prosthetic implant is about 12 years. The most common reason of failure of total joint prosthesis is aseptic loosening and in this case it is essential to replace the loosened prosthesis. Aseptic loosening of bone cement occurs because of lack of chemical bonding, mechanical failure of the cement, fibrous tissue formation resulting from heat induced necrosis and osteolysis induced by wear debris particles [2]. Loosening can occur in prosthesis-cement or cement-cement or bone-cement area. Failure at the prosthesis-cement interface occurs when relative motion exists between these two components. In the total hip system this occurs often when femural metal component is used. Failure within the cement is because of fracture of the cement. Failure at the bone-cement interface is the most common cause of loosening which may be due to the behavior of living tissue in direct contact with the foreign surface of the implant.

1.8.2 Porosity

Porosity is one factor that decreases mechanical properties and makes the bone cement susceptible to fracture and failure. Pores behave as stress riser and initiate crack formation. There are two types of pores in bone cements, which are macropores (pore diameter > 1 mm) and micropores (pore diameter ≈ 0.1 – 1 mm). Porosity may develop because of air initially present in the powder part, entrapment of air during mixing and delivery of the cement to the implant site, shrinkage of the materials during polymerization, monomer evaporation during curing reaction. A pre-mixed material, for example, solution of polymer in monomer is used in literature in order to minimize porosity formation. It is also reported that compared to hand mixing, cement porosity can be decreased by vacuum mixing and by centrifugation [8].

1.8.3 Residuals

Content of residuals depends on monomer composition, polymerization temperature, accelerator and initiator. Glass transition temperature (T_g) is also a parameter affecting presence of residual monomers. For a PMMA bone cement, T_g is about 90 to 115ºC and the polymerization reaction of bone cement is completed at about 10ºC below this value. The free volume of polymer decreases below T_g and prevent monomer diffusion to the radical ends of the polymer chain, therefore, polymerization can not reach entire completion [25]. It

was reported that PMMA bone cement contains about 3% residual MMA [26] and 0.1 to 0.5% tertiary aromatic amines [27]. Unreacted MMA affects the degree of polymerization and average molecular weight of the polymer; therefore presence of monomer can affect the mechanical properties of the cement. As residual monomer content increases, the length of polymer chains in the bulk will decrease and so the strength of cement will also decrease [28]. In addition, residual monomer acts as a plasticizer and causes a decrease in mechanical properties. If the residual methyl methacrylate monomer releases, it is toxic to bone cells and causes chemical necrosis. It was stated that methyl methacrylate may affect the local blood circulation causing a sudden decrease in the blood pressure of the patient.

Trap et al. developed a bone cement using methyl methacrylate / n-decyl methacrylate / isobornyl methacrylate (MMA/DMA/IBMA) monomers and dimethyl-p-toluidine (DMPT) / dihyroxypropyl-p-toluidine (DHPPT) accelerator system. It was reported that there was about 10 to 15 fold reduction in residual MMA and about 3 to 4 fold reduction in aromatic amine amounts. Residual content of DMA and IBMA monomers were reported as 0.35% and 0.66%, respectively [25].

1.8.4 Sterilization Methods

Different commercial cement formulations are sterilized by different methods; for example, Simplex-P and Palacos R are sterilized by gamma irradiation and ethylene oxide (EtO) treatment, respectively. Sulfix®-60 and Duracem 3 are sterilized with formaldehyde tablets. Sterilization method of the powder constituents of the cement affects the mechanical properties of bone cement. It was stated that gamma sterilization of a conventional bone cement formulation caused a significant decrease in the flexural fatigue performance of the cement. Gamma irradiation or EtO did not cause statistically significant effect on quasistatic tensile and compressive properties of Palacos R, but molecular weight and uniaxial tension–compression fatigue performance of the gamma sterilized cement were found to be significantly lower than EtO sterilized or unsterilized cement. Formaldehyde did not affect mechanical properties [29].

1.9 Setting Properties of Bone Cement

During the preparation of bone cements, solid and liquid parts are mixed till a homogenous dough is formed. There are some periods starting from the mixing till the dough solidifies. Dough time, working time and setting time are these periods used to characterize setting properties of the bone cements. Dough time is the period between the beginning of mixing to the point when the bone cement mixture will not stick to non-powdered surgical latex gloves. Dough time is approximately 2 to 3 minutes after the beginning of mixing for most PMMA cements. Dough time is a function of the surface area of the polymer powder; as the total surface area increases dough time gets shorter [30]. Working time is the time from the end of dough time until the cement is too stiff to manipulate. It is the interval between dough and set time and usually takes 5 to 8 minutes. Setting time is the period measured from the beginning of mixture until the surface temperature of the dough mass is one-half of its maximum value. It is the sum of the dough time and the working time and it is typically 7 to 11 minutes. At setting time, the cement would no longer plastically deform under hand pressure. Setting time depends on powder-to-liquid ratio, temperature of the cement and ambient temperature [31]. Dough time, working time and setting time are summarized in Figure 1.10 [32].

There are some factors that affect the curing of PMMA for example:

1. More rapid mixing shortens the dough time,
2. Higher room temperatures shortens both the dough and setting times,
3. Increased humidity shortens setting time [32].

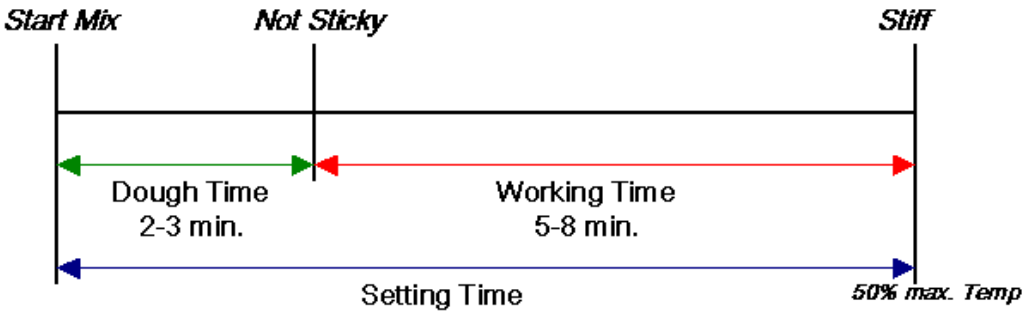

Figure 1.10 Illustration of dough time, working time and setting time

Shulin et al. showed that vacuum mixing decreased the setting time of the bone cement due to a decrease in oxygen content in the mixer. They stated that oxygen content in the mixture had a significant effect on setting time of bone cement; oxygen behaved as a radical scavenger, reacted much more rapidly with the free radicals than MMA, lowered the free radical concentration and extended the setting time. They didn't observe any effect of oxygen on dough time and maximum curing temperature [33].

Milner developed a theoretical relationship between setting time, ambient temperature and amounts of initiator and activator. It was reported that dough time was not affected by the amounts of DMPT activator and BPO initiator; it was dependent on the diffusion of monomer into the polymer beads of powder component when a critical swelling of the polymer powder was reached. In addition; as the amounts of initiator and activator increased, the rate of polymerization, heat production and the peak temperature increased. It was indicated that setting time depended on temperature since parameters that influence setting time such as polymerization, swelling and dissolution of polymer particles change with temperature [11].

Meyer et al. studied the effects of thickness of the cement, powder to liquid ratio and ambient temperature on the setting properties of Simplex-P acrylic bone cement. It was reported that maximum temperature reached 70ºC at the bone-acrylic interface and as the thickness increased and powder-to-liquid ratio decreased, maximum temperature and setting time increased. Moreover; when the ambient temperature increased, the maximum curing temperature also increased while the dough time, working time and setting time decreased. Change in powder-to-liquid ratio did not affect the working time but increase in ambient temperature and mass of the cement caused a decrease in working time [31].

1.10 Shrinkage

Volume of the cement changes during polymerization; first the mixture shrinks, then it expands during heat release and finally shrinks again during cooling. Shrinkage is observed during polymerization of MMA because of the conversion of double bond to a single bond between carbons and leads to difference in the densities of MMA and PMMA. Densities of MMA and PMMA are 0.94 and 1.18

g/mL, respectively. Approximately, there is 21.1% shrinkage when MMA polymerizes to PMMA [34]. Shrinkage may lead to residual stresses in the cement therefore porosity and probability of fracture can increase and also it may influence loosening of the prosthesis. In order to solve this problem PMMA powder is used in bone cements to minimize shrinkage-strain during the polymerization of MMA.

Silikas et al. stated that shrinkage-strain was dependent on degree of conversion of monomer. While the degree of conversion decreases the shrinkage-strain value reduces [34]. Oldfield and Yasuda reported that there was a decrease in shrinkage-strain with increasing amine concentration; the presence of excess amine leads to formation of nitroxides and inhibites the polymerization of MMA [35].

1.11 Thermal Properties of Bone Cement

Acrylic bone cements set by an exothermic polymerization reaction. It was stated that the maximum temperature is a function of:

- The total amount of heat produced by polymerization reaction
- The rate of heat production
- The effective thermal conductivity (κ) and heat capacity of bone, prosthesis and cement
- The initial conditions of prosthesis-cement-bone system

The amount of heat produced by the cement depends on the amount of monomer used and the thickness of the cement. As monomer-to-polymer ratio decreases the amount of polymerization and so heat generated decrease since the amount of polymerizing monomer is reduced while the viscosity of the cement increases. Increase in viscosity leads to difficulty in workability and application of the cement. Typical thicknesses of bone cement in hip replacements are reported to be 2-5 millimeters, with some areas as thick as ten millimeters**.** Meyer et al. observed that for a cement mantle of 10 mm the maximum temperature was 107ºC and for a mantle of 3 mm it was 60ºC [31]. Sih et al. observed that the temperature was 41ºC for a cement thickness of 1 mm, 56ºC for 5 mm and 60ºC for 6-7 mm [36]. The rate at which heat is produced changes with the reaction rate which depends on temperature of the

cement and heat dissipation of cement's surrounding. The effective thermal conductivity (κ) and heat capacity change according to material that is used as implant. The thermal conductivity (κ) and heat capacity of bone depend on the density of the bone and the amount of functional vasculature. Bone cement in form of a large sphere will reach to higher temperatures than a thin sheet form due to poor thermal conductivity of polymers [31]**.** In addition; the initial conditions are important such as temperatures of the medium and the components. There were several attempts in order to lower the curing temperature of the bone cement. DiPisa et al. decreased the temperature at the bone-cement interface from 70ºC to 49ºC by cooling the acetabular socket to –84ºC before the operation [37]. As it was mentioned previously, curing temperature depends on the ambient temperature and Dunne et al. found that the maximum temperature was 53ºC at an ambient temperature of 4ºC and increased to 125ºC when the ambient temperature was 37ºC [38].

In addition, presence of a chain stopping agent affects the peak temperature of the bone cement. Sufficient amount of chain stopping agent prevents the formation of long-chain high molecular weight macromolecules during the polymerization of the acrylic monomer and controls the setting of the cement preventing formation of a highly exothermic reaction [39].

In the literature there are some bone cement compositions in which polymer-monomer syrups are used. These compositions have a convenient viscosity for handling and reduce curing period for in vivo applications, heat evolution during polymerization, and shrinkage [16].

Particle size of the PMMA powder is another important parameter which affects the curing temperature. It was reported in the literature that the use of PMMA powder with average diameter of 60 μm reduced the maximum temperature by more than 30°C compared to the formulations with smaller PMMA particles [12].

1.12 Mixing Methods

Cement mixing methods have considerable effect on physical and mechanical properties of the bone cement. In addition; other properties such as dynamic viscosity, static compressive modulus, static ultimate compressive strain, and creep are affected by mixing methods. Viscosity is important in deciding the

suitable mixing system and conditions for a particular cement. Swelling of the polymer particles in the monomer and polymerization of the monomer are the causes of the increase in viscosity. Swelling and polymerization depend on temperature so does viscosity and it was stated that at higher temperatures the rate of increase in viscosity increases [13]. Cement viscosity should be low enough to allow the dough easily pass through delivery system, flow and penetrate into the interstices of the bone surface in a short time since bone cement is pseudoplastic. Dynamic viscosity decreases with an increase in shear rate and increases with an increase in time as polymerization goes on [8].

Mixing methods include hand mixing, centrifugation, vacuum mixing and combined mechanical mixing. In hand mixing, the powder component is added to the liquid in a polymeric, usually poly(propylene) (PP), bowl. Then these components are stirred, using a PP spatula, at 1 Hz [40] or 2 Hz [41] for a period of time between 45 s or 120 s [42, 43].

In centrifugation mixing, the hand-mixed dough is poured into a syringe from which the nozzle had been detached. The syringe is then immediately placed in a centrifuge and spun at a maximum speed of between 2,300 rpm [44] or 4,000 rpm [41] for a time between 30 s [44] or 180 s [45].

In vacuum mixing, different proprietary and experimental chambers are used, the proprietary ones include; the Simplex Enhancement Mixer (Howmedica, Rutherford, NJ, USA), Stryker High Vacuum System (Stryker, Kalamazoo, USA), MITAB (Mitab, Sjobo, Sweden), Optivac (Mitab, Sjobo, Sweden), Stryker Mixevac II (Stryker, Kalamazoo, USA), Sterivac (SD, Germany), Mitvac, Cemvac Merck, Bonelock and Cemex systems [8]. There are no general steps in vacuum mixing; each type has its own instructions.

CHAPTER 2

LITERATURE REVIEW

2.1 Modified Acrylic Bone Cements

Studies on bone cements are going on since 1930's. Recent studies include modifications of acrylic bone cements either by adding some ingredients or altering the preparation parameters.

Wijn prepared acrylic bone cements composed of PMMA polymer powder and liquid monomer mixed with an incompatible high viscosity aqueous gel which was soluble in body fluids and dissolved after implanting. This led to a porous structure in bone cement and so tissue invasion. Maximum temperature during setting was reduced but mechanical strength of this bone cement was less than the mechanical strength of conventional bone cements [46].

Cervantes et al. prepared bone cement samples using MMA as the base monomer and by using methacrylic acid (MAA), diethyl amino ethyl methacrylate (DEAEM), 4-methacryloyloxybenzoic acid (MBA) or 4-diethyaminobenzyl methacrylate (DEABM) as comonomers at various molar fractions and compared their properties. It was reported that bone cements prepared with the aromatic monomers provided more hydrophilic cements than their aliphatic counterparts for low concentrations of the functional monomer. It was also found that bone cements prepared with high amounts of the acidic aliphatic monomer provided the highest exotherm of reaction and shorter setting times than MBA based cements. On the other hand, DEABM containing bone cements exhibited shorter setting times than DEAEM formulations and slightly higher peak temperatures. It was reported that when aromatic methacrylates were used at 0.05 molar fraction, the highest tensile and compressive strengths were found as 46 MPa and 118 MPa, respectively for MBA and 51 MPa and 108 MPa for DEABM formulations. Further increase in the aromatic monomer concentration led low mechanical properties due to solubility problems. It was concluded that the

addition of aromatic structures improved the mechanical properties of bone cements as long as the monomer is soluble in MMA [24].

Vàzquez et al. added β-Tricalcium phosphate, $Ca_3(PO_4)_2$, (TCP) encapsulated with poly(ethylene glycol) (PEG) to PMMA bone cement in order to improve stability of cement in long term. TCP is incompatible with PMMA, therefore it was encapsulated with PEG in order to enhance compatibility. It was reported that addition of TCP-PEG particles did not affect maximum temperature, setting time and mechanical properties significantly, but decreased dissolution of bioceramic particles in SBF (simulated body fluid). After 3 months of storage in SBF, compressive strength values were in the range of 76–78 MPa, higher than the minimum required value by ISO 5833 (70 MPa) and tensile strength values were in the range of 42–48 MPa, higher than the minimum value reported for commercial formulations (30 MPa) [47].

Pascaul et al. prepared bone cements by the substitution of high percentages of methyl methacrylate (MMA) up to 60% (v/v) by a higher molecular weight and more hydrophilic monomer, ethoxytriethyleneglycol methacrylate (TEG). It was stated that bone cements prepared with replacement of MMA by about a 30% (v/v) TEG showed an improvement in properties with respect to bone cements based on PMMA. Maximum temperature was decreased from about 84°C to 64°C, residual monomer was decreased, setting time was extended and mechanical strength values were in acceptable range. As the TEG concentration was increased up to 60% (v/v), mechanical strength was reduced [48].

Kuo et al. synthesized chitosan microspheres by reacting chitosan with β-tricalcium phosphate (β -TCP) and glutaraldehyde with a crosslinking reaction in the oil phase and then prepared poly(methyl methacrylate) (PMMA) bone cement composites in the presence of 0, 50, and 66.7% chitosan/β-TCP microspheres. Chitosan [poly(1,4)-β-d-glucopyranosamine] is a natural polysaccharide, which can be obtained from marine and terrestrial invertebrates and lower forms of the plant kingdom. Chitosan is a biodegradable, biocompatible, and nontoxic biopolymer which can be manufactured into different shapes and it is becoming a promising material in biomaterial applications. It was stated that the addition of chitosan/β-TCP microspheres into the prepared bone cements decreased the ultimate tensile strength, while the modulus remained the same, decreased curing temperature, improved the handling property of the cement paste such as

increase in setting time and less stickiness behavior of the paste. According to the scanning electron micrograph observations, it was claimed that chitosan/β-TCP microspheres completely mixed with bone cement powder and it was suggested that the prepared composites could provide scaffold for growth of osteoblast cells [49].

Méndez et al. prepared bone cements by incorporation of different amounts of a methacrylic monomer derived from vitamin E (MVE) and used 4-N,N-dimethylamino benzyl alcohol (DMOH) accelerator instead of DMPT due to its lower toxicity. MVE is a natural biological antioxidant which prevents peroxide reactions and protects cells from hazardous effects of free radicals. It was reported that addition of increasing concentrations of MVE, decreased peak temperature from 62ºC to 36ºC and increased setting time from 17 to 25 minutes. It was stated that compressive properties were in acceptable range however addition of 25 wt% MVE led to a significant decrease in tensile properties. It was concluded that cements containing 15-25 wt% MVE provided the best biocompatibility results compared to the other compositions [50].

2.2 Additives

2.2.1 Radiopaque particles

Acrylic bone cements are used in orthopedic surgery to fix implants, it is essential to monitor implant after surgery for the control of healing process. The bone cement is radiolucent and transparent to X-rays. Radiopacity of commercial bone cements was provided by the addition of 8-13% (w/w) barium sulphate ($BaSO_4$) or 9-15% (w/w) zirconium dioxide (ZrO_2). It was reported that bone cements with zirconium dioxide have higher opacity than those containing barium sulphate [51].

Addition of inorganic radiopacifying particles affects the mechanical and biological properties of bone cement. It was reported that about 10% (w/w) $BaSO_4$ addition improved the resistance towards fatigue crack propagation. On the other hand, addition of $BaSO_4$ reduced the tensile strength while the reduction was lower when ZrO_2 was added [51].

Radiopacifiers have a higher density and polarity than the polymeric material and they tend to collect together and clump or agglomerate in the bone cement.

These agglomerates have been shown to act as stress concentration sites and they decrease the ultimate flexural strength, ultimate tensile strength, fatigue strength, as well as the fracture toughness of the cement. Demian et al. microencapsulated the radiopacifier with a bone cement compatible material prior to being added to the powder part of bone cement composition. It was stated that when the powder part combined with the liquid monomer, the bone cement compatible material dissolved and released the radiopacifier particles into the bone cement matrix. Therefore, the radiopacifier was prevented from agglomerating in the cement and the radiopacifier particles became dispersed throughout the bone cement matrix which increased the fatigue life of the cement [52].

Caravia et al. stated that when the radiopaque particles enter the joint space they may cause damage to the articulating surfaces with a marked increase in the production of polyethylene wear debris and because of its abrasive properties, zirconium dioxide is more harmful than barium sulphate [53]. Some studies have proved that the addition of radiopaque particles to bone cement enhances the macrophague-osteoclast differentiation and therefore they may contribute to the bone resorption and aseptic loosening [54]. Lack of adhesion between inorganic radiopaque particles and polymer matrix may be the reason of reduction of mechanical strength of bone cement since the interface is very important for efficient stress transfer from the matrix to the fillers [55]. Researches have been carried out to provide radiopacity by using an X-ray opaque iodine containing methacrylate in the liquid phase of the bone cement and 2,5-diiodo-8-quinolyl methacrylate (IHQM) was proposed as the new radiopaque agent. It was reported that this monomer caused a decrease in peak temperature and a slight increase in setting time with the desired radiopacity of bone cement [56].

Hooy-Corstjens et al. prepared bone cement in which an iodine-containing methacrylate copolymer; a copolymer of methyl methacrylate and 2-[4-iodobenzoyl]-oxo-ethylmethacrylate (4-IEMA) was added to the powder component of the cement to provide radiopacity. It was stated that the intrinsic mechanical behavior of the iodine containing cement was better than $BaSO_4$ containing cement. Concerning the fatigue behavior it was concluded that, though $BaSO_4$-cement had a slightly higher fatigue crack propagation resistance than iodine-cement, the fatigue life of vacuum-mixed iodine-cement was

significantly better than that of $BaSO_4$-cement. This was explained by the presence of $BaSO_4$ clumps in the commercial cement which acted as crack initiation sites [57].

2.2.2 Hydroxyapatite (HA)

It is known that calcium phosphate with a Ca:P ratio of 1.0 to 2.0 is biocompatible and HA is a ceramic with Ca:P ratio of 1.62 having a composition similar to natural bone. Chemical structure of pure HA is $Ca_{10}(PO_4)_6(OH)_2$. Its surface is highly reactive and lead to favorable attachment and bioactivity; it has osseoconductive and osseoinductive effects [9]. Therefore, attentions were drawn to investigations about effects of HA addition on properties of bone cements.

Although hydroxyapatite is highly bioactive, there exist some disadvantages such as brittleness of the resulting porous cement, difficulties of setting in vivo, wash out of implanted cement paste and relatively low strength [2]. It would be advantageous for a bone cement to have biocompatibility of HA and strength and setting characteristics of PMMA cements.

In 2004 McGee et al. invented biocompatible, fast setting, strong, durable bone cement compositions which included calcium phosphates and one or more biocompatible cements such as calcium aluminates with anion donating accelerators. It was reported that calcium phosphate provided biocompatibility and other biocompatible cements increased the strength of the bone cement. It was stated that calcium phosphate-calcium aluminate cement compositions did not release energy rapidly and during setting of the cement the temperature rise was about 45ºC. For these cements, it was reported that as the calcium phosphate concentration was increased the strength was reduced [58].

Moursi et al. investigated the effect of incorporation of HA in PMMA matrix on biological properties of osteoblast response. It was reported that addition of HA improved osteoblast response as compared to PMMA alone [59].

Mechanical properties of PMMA-HA composites have been studied by many researchers. It was stated that addition of up to 40 wt% HA to bone cement increased the fracture toughness, addition up to 15 wt% increased flexural modulus and did not cause a change in tensile and compressive strengths. In

addition; it was stated that HA acted as a heat sink by absorbing the released heat and resulting lower curing temperature [9].

Vallo et al. modified a commercial acrylic bone cement by adding different weight fractions of polycrystalline hydroxyapatite and investigated mechanical properties of them. It was stated that maximum 15 wt% HA could be added to obtain higher values in flexural modulus and fracture toughness. Further addition of HA significantly lowered the workability characteristics [60].

Morita et al. developed acrylic bone cements containing MMA and 4-methacryloyloxyethyl trimellitate (4-META) as monomers, tri-n-butyl borane (TBB) as an initiator and PMMA powder. 4-META was used as an adhesion promoting agent therefore prepared cement could adhere to bone and prosthesis. In addition hydroxyapatite particles were added as bone compatible filler. They observed that as the amount of HA increased in the absence of 4-META, the values of tensile strength and bending proportional limit decreased and then addition of 4-META improved the mechanical properties of the cement. They stated that the improvement in mechanical strength of HA containing 4-META cement is because of adhesion between the HA particles and cement matrix. HA particles did not affect the adhesion of the 4-META cement to bone and metals [61].

Serbetci et al. prepared acrylic bone cements with incorporation of various amounts of HA. It was reported that maximum curing temperature was decreased from 111°C to 87°C with the addition of HA up to 10%. HA addition also increased compressive strength from 96 MPa to 122 MPa [62].

2.2.3 Antibiotics

After joint replacements some complications such as infection may occur due to heat release, toxicity of monomer and bone tissue change related to surgery. Therefore, antibiotic loaded bone cements can be used to overcome this problem. Gentamicin was first added to standard cement by Buchholz and Engelbrecht for the prophylactic treatment of infection due to its wide-spectrum antimicrobial activity, its excellent water solubility, its thermal stability and its low allergenicity. Passuti et al. reported that the infection rate was decreased from 6% to 1.6% for gentamicin loaded bone cements [63]. Other heat stable antibiotics such as tobramycin, erythromycin, vancomycin, clindamycin in

powder form can also be used. Addition of antibiotics did not have a significant effect on the mechanical properties of bone cement [64].

2.2.4 Fibers

In general, bone cements are weaker in tension than in compression. In order to improve mechanical strengths, various biocompatible and chopped fibers were added into the cement formulations and their effects on mechanical properties were examined. It was shown that addition of graphite or carbon fibers increased the tensile strength [65], the fatigue life and fracture toughness of the bone cement [66]. Wright et al. prepared bone cements with the incorporation of Kevlar aramid fibers and observed that addition of 7 wt% Kevlar aramid fiber caused 32% increase in strength and 74% increase in fracture toughness. On the other hand it was reported that mixing process of the cements which contained fiber higher than 7 wt%, was very difficult [67].

Furthermore; presence of inorganic fillers like short carbon fibers increase stiffness and decrease molecular mobility under an acting load therefore reduces the creep. It was stated that addition of 2 wt% short carbon fibers were very effective in mechanical properties however they had reverse effect on the flow characteristic of the cement in the doughy state. Addition of particulate fillers or short polyethylene fibers increased fracture toughness by keeping the working time and curing characteristics acceptable [68].

2.3 Aim of the Study

The aim of this study was to prepare new formulations for acrylic bone cements with the desired thermal and mechanical properties. For this purpose; the following steps were followed:

1. Preparation of PMMA microspheres by suspension polymerization
2. Preparation of new formulations for acrylic bone cements by using PMMA microspheres and MMA monomer
3. Modification of the compositions by adding constituents such as hydroxyapatite, barium sulphate and 1-dodecyl mercaptan
4. Examination of the effects of hydroxyapatite, barium sulphate and 1-dodecyl mercaptan addition on mechanical and thermal properties of bone cements
5. Optimization of the parameters affecting the properties.

CHAPTER 3

MATERIALS AND METHODS

3.1 Materials

Methyl methacrylate monomer (MMA), 1-dodecyl mercaptan (DDM) and Poly(vinyl alcohol) (PVA) were obtained from Acros Organics (USA), N,N-dimethyl-p-toluidine (DMPT) and benzoyl peroxide (BPO) were obtained from Sigma-Aldrich Chemie (Germany). Hydroxyapatite (HA) was purchased from Riedel-de Haën A.G. (Germany). Cemex bone cement is a product of Tecres SPA (Italy). Sodium hydroxide (NaOH) was supplied by J. T. Baker (Holland) and barium sulphate ($BaSO_4$) was obtained from Merck (Germany). Ethanol was technical grade and product of Tekel Sincan Organize Sanayi (Turkey).

All chemicals, except MMA, were used as obtained without further purification. MMA contains hydroquinone as inhibitor to prevent premature polymerization therefore prior to polymerization reaction, it was washed with 10 wt% aqueous sodium hydroxide solution to remove the inhibitor.

3.2 PMMA Microsphere Preparation

PMMA microspheres were prepared by suspension polymerization of MMA. The polymerization of MMA was carried out in ethanol/water (50/50 v/v) media by using BPO as initiator and PVA (M.W. 88.000) as stabilizer. BPO initiator (160 mg) was dissolved in MMA (16 mL) monomer and nitrogen gas was purged through the solution for 15 minutes to exclude air. Distilled water (80 mL), ethanol (80 mL) and of aqueous PVA solution (24 mL, 5% w/v) were mixed in a 500 mL round bottom two necked flask fitted with a nitrogen inlet and condenser. Nitrogen gas was bubbled through the solution for 15 minutes. Then monomer solution was added to the flask and nitrogen was bubbled for 15 more minutes. The flask was immersed in an oil bath at 70ºC temperature and the polymerization medium was mixed with a magnetic stirrer during the reaction.

Nitrogen purging through the solution was continued during all process to exclude air from the medium to prevent its inhibition effect on the polymerization of MMA monomer. The medium was homogenous and clear at the beginning of the polymerization since the monomer is soluble in alcohol. However after 10-15 minutes solution became white opaque because of formation of PMMA microspheres. The reaction continued for 6 hours at 70°C and then was stopped by sudden cooling. Formed PMMA microspheres were filtered, washed with water and alcohol and then dried in vacuum oven. All materials and their amounts used in the suspension polymerization of MMA are given in Table 3.1.

Table 3.1 Amounts of materials used in polymerization

Materials	Amount (mL)	Amount (g)	Wt%
MMA	16	15,04	8,2
Ethanol	80	63,2	34,4
H_2O	104	104	56,6
PVA[a]	-	1,2	0,7
BPO	-	0,16	0,1

[a] PVA, MW = 88,000 g/mol

The dried PMMA microspheres were weighed in an electronic balance and the yield was calculated by using the following equation:

Yield% = [(wt of dried PMMA microspheres) / (wt of MMA)] x 100

Microspheres were prepared as few batches and then combined as the stock source. For all preparation processes the yield values were found to be higher than 90%.

3.3 PMMA Microsphere Characterization

Chemical structures of the synthesized PMMA microspheres were analyzed by Fourier Transform Infrared Spectrometer (FTIR) and Nuclear Magnetic Resonance Spectrometer (NMR). Topographic shapes and size distribution analysis were carried out by using Scanning Electron Microscopy (SEM) and Particle Size Analyzer, respectively.

3.3.1 Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of the microspheres were recorded by using a FTIR spectrometer (Perkin Elmer 1600 Series FTIR). KBr pellets were prepared by mixing the microspheres and potassium bromide (KBr). The mixture was pressed to form a pellet, and the spectrum was recorded over the wave number range from 1000 to 4000 cm^{-1}.

3.3.2 Nuclear Magnetic Resonance (NMR) Spectroscopy

Solid state ^{13}C-NMR spectra of PMMA microspheres were obtained using cross polarization-magic angle spinning (CP/MAS.DD) on a Bruker Superconducting FT.NMR Spectrometer Avance TM 300 MHz WB (Germany). High power Ultrashield superconducting magnet with 4 mm MAS prob was operated at a carbon frequency of 75.38 MHz and proton frequency of 299.77 MHz. Liquid state ^{1}H-NMR spectra of the PMMA microspheres were obtained using Bruker-Spectrospin Avance DPX 400 Ultra-Shield liquid-solid NMR. Deuterated chloroform ($CDCl_3$) solvent was used for ^{1}H-NMR analysis.

3.3.3 Scanning Electron Microscopy Analysis (SEM)

Topographic shapes and average particle size and size distributions of PMMA microspheres were examined by Scanning Electron Microscopy (SEM) (JEOL, JSM-6400, NORAN Instruments, Tokyo, Japan). Average particle size of PMMA microspheres was measured on the photographs. In addition; fracture surfaces of tension samples were also examined by SEM.

3.3.4 Particle Size Analysis

The average particle size and size distributions of PMMA microspheres was examined by Zeta Sizer (Malvern Nano ZS90, UK). Distilled water was used as a dispersant and the analysis was performed at 25°C.

The average particle size and size distributions of HA and $BaSO_4$ were examined by particle size analyzer (Malvern TM Mastersizer, Malvern Instruments Ltd, UK). For this purpose HA was sieved through 150 μm mesh while $BaSO_4$ was used as obtained and distilled water was used as dispersant for both cases.

3.4 Bone Cement Preparation

Bone cement is a two component system and it is obtained by mixing the liquid and the powder parts. Liquid part was prepared by mixing MMA monomer and DMPT accelerator and also various amounts of 1-dodecyl mercaptan was added to some compositions as chain stopping agent. Powder part consisted of PMMA polymer and BPO initiator. Moreover, powder part of some compositions included various amounts of HA and $BaSO_4$. First, all constituents of powder part such as PMMA, HA, $BaSO_4$ were weighed and mixed in a poly(propylene) cup to provide homogeneity. Liquid part composed of MMA, DMPT and DDM were weighed and stored in a dark glass bottle until use. Prior to experiments all materials were kept at room temperature at least for one hour to provide thermal equilibrium. To prepare the cement dough, liquid part was poured into the powder and mixed with a spatula for 2-3 minutes until a homogenous dough was formed. All bone cements were prepared by hand mixing.

In each preparation, 6 mL MMA monomer was used for 4 g PMMA polymer and this ratio was kept constant. In addition, in all experiments 45 mg BPO initiator and 56 µL DMPT accelerator were used. Different compositions were prepared by adding various amounts of HA, DDM and $BaSO_4$. Compositions prepared in this study are given in Table 3.2.

Table 3.2 Bone cement compositions

	Powder Part				Liquid Part		
Sample	PMMA (g)	BPO (mg)	HA (mg)	$BaSO_4$ (mg)	MMA (mL)	DMPT (µL)	DDM (µL)
BC1	4.0	45	-	-	6	56	-
BC2	4.0	45	168	-	6	56	-
BC3	4.0	45	348	-	6	56	-
BC4	4.0	45	-	604	6	56	-
BC5	4.0	45	348	604	6	56	-
BC6	4.0	45	348	604	6	56	66.4
BC7	4.0	45	348	604	6	56	132.8
BC8	4.0	45	348	604	6	56	199.3

Polymer-to-monomer ratio, BPO and DMPT amounts were kept constant in all compositions. (d_{MMA}=0.93 g/mL, d_{DMPT}=0.937 g/mL, d_{DDM}=0.84 g/mL

The mechanical and thermal properties of a commercial bone cement, Cemex Isoplastic (high viscosity), was also examined. Cemex Isoplastic bone cement is composed of 40 g powder part and 13.3 g liquid part while the polymer-to-monomer ratio is 2.56. The composition of Cemex bone cement is given in Table 3.3.

Table 3.3 Cemex Isoplastic composition

Powder Part			**Liquid Part**			
Material	**Wt%**	**Amount (g)**	**Material**	**Wt%**	**Amount (g)**	**Amount (mL)**
PMMA	84.3	33.72	MMA	99.10	13.18	14.17
BPO	2.7	1.08	DMPT	0.90	0.12	0.13
$BaSO_4$	13	5.20	HQ	75 ppm	75 ppm	75 ppm

3.5 Bone Cement Characterization

Tension and compression tests were performed to examine mechanical properties of the prepared bone cement samples. Mechanical tests were performed by using LLoyd® LRX 5K (LLoyd Instruments Limited, Fareham, Hampshire, UK) testing machine with a cell load of 5000 Newton at room temperature.

3.5.1 Tension Tests

Tension test samples were prepared as follows; bone cement dough was homogenously laid on a polyethylene surface by the help of a polyethylene cylinder. Dog bone shaped test samples were cut by a knife while the dough was still soft. The samples were allowed to cure for one hour and then they were kept in a saline solution in a temperature-controlled water bath for 24 h at 37±1°C. The samples were taken out from the water bath, their thickness and width were measured and load applied areas were calculated. The tension tests were performed with a cross-head speed of 1 mm/min at room temperature. Tension test samples and test set up are shown in Figure 3.1. Young's modulus and ultimate tensile strength values were calculated from load versus displacement curves. For each sample at least five specimens were tested and the average values were taken.

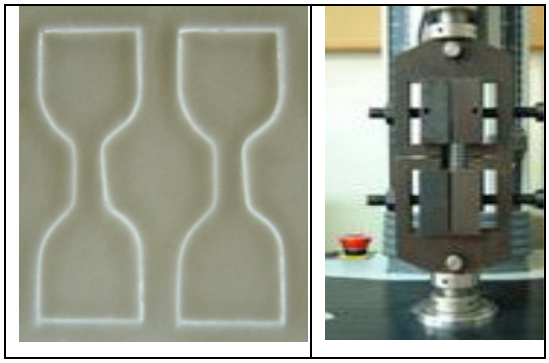

Figure 3.1 Tension test samples and test set up

3.5.2 Compression Tests

In the preparation of compression test samples, a stainless steel compression mould, which complies with ASTM standard F451-95 (Standard specification for acrylic bone cement), was used. The mold was composed of three cylindrical plates which have 84 mm diameter and 12 mm height and one of the plates had 52 holes each having 6 mm diameter.

The prepared dough was placed in the mould and pressed with the help of two clamps. The dough was allowed to cure for one hour and then the specimens were removed from the mould, kept in a saline solution in a temperature-controlled water bath for 24 h at 37±1°C. Then they were subjected to the compression test. Prior to test, the diameter and gauge lengths of specimens were measured and the load applied areas were calculated. The compression tests were performed with a cross-head speed of 25 mm/min at room temperature. The compression mould and compression test set up are shown in Figure 3.2. Young's modulus and ultimate compressive strength values were calculated from load versus displacement curves. For each sample at least eight specimens were tested and their average values were obtained.

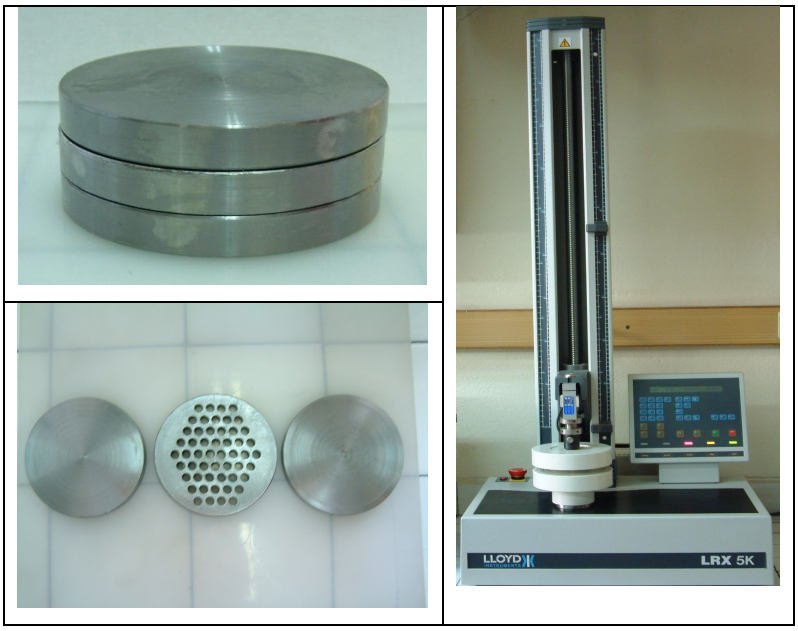

Figure 3.2 Compression mould and test set up

3.5.3 Thermal Analysis

The maximum curing temperatures of bone cements were measured by a "Thermocouple Input Module" (SuperLogics, USA). J-type thermocouples working in the temperature range of -210°C~760°C were used. The positive conductor of the thermocouple is made of iron, and the negative conductor is made of constantan. Thermocouples were cut into pieces with 5 cm in length and removed from isolators. Then they were rolled with Teflon band and one end of the thermocouple was electrically welded.

The temperature measurement experiments were performed at 23 ± 2ºC. The cement dough was prepared and rounded to give a spherical shape with a radius of ~15 mm. Then the welded end of the thermocouple was placed in the centre of the dough. The temperature was recorded for 1200 seconds with a 1 data per second record rate.

Peak temperature was the maximum temperature reached during the polymerization. Setting time of bone cement was defined as the time when the temperature rise was at halfway point between the maximum temperature and the ambient temperature [69]. Setting temperature can be calculated by using the following equation:

$$T_{setting} = T_{ambient} + T_{maximum} / 2$$

A typical temperature versus time graph showing the exothermic temperature changes occurring in acrylic cements during the setting process is given in Figure 3.3.

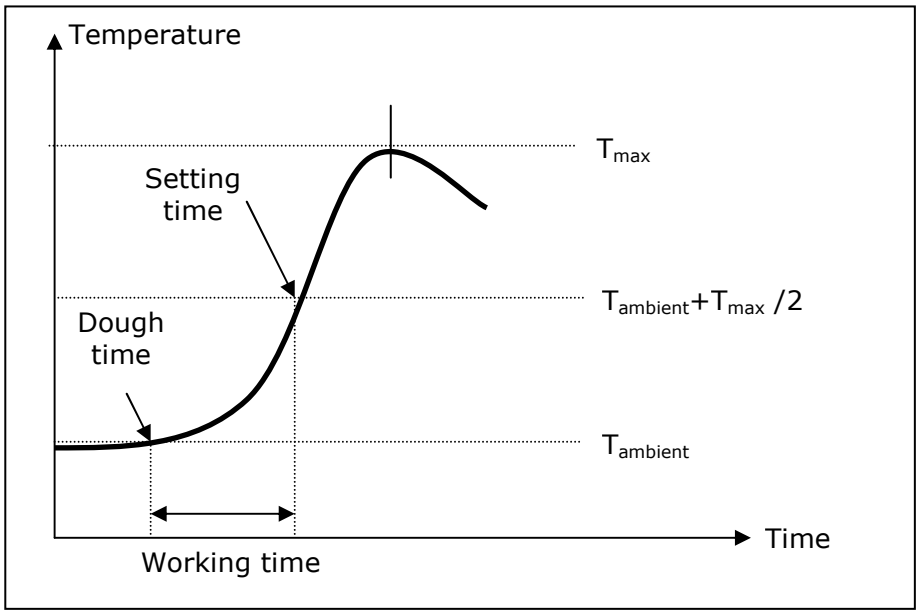

Figure 3.3 Typical temperature versus time graph [31]

CHAPTER 4

RESULTS & DISCUSSION

4.1 FTIR Analysis

FTIR spectrum gives the details of functional groups. The IR spectrum of the prepared PMMA microspheres is shown in Figure 4.1. The sharp intense peak seen at 1731 cm^{-1} can be identified as C=O stretching vibrations in the pendant group (-$COOCH_3$) of PMMA. Absorption bands in the range of 1500-700 cm^{-1} come from the following vibration modes; the C-O (ester bond) stretching vibration (1064-1242 cm^{-1}), C-H bending vibration (1450-1388 cm^{-1}), CH_2 rocking vibration (810 and 752 cm^{-1}). The broad peak from 2845 to 2998 cm^{-1} is due to the presence of C-H stretching vibrations. It can be concluded that the prepared PMMA microspheres demonstrate the characteristic peaks of pure polymer of PMMA.

4.2 NMR Analysis

4.2.1 ^{13}C-NMR

^{13}C-NMR spectra of PMMA microspheres are shown in Figure 4.2. The main characteristics of the ^{13}C-NMR spectra of the PMMA microspheres are the peaks corresponding to the methyl carbon (CH_3–) at 17–21 ppm, the methoxy carbon (CH_3O–) at 51.27 ppm, the quarternary carbon (C_α) around 45 ppm, the methylene carbon (–$C_\beta H_2$–) between 52–58 ppm and the carbonyl carbon groups (–C=O) at 176.9 ppm.

4.2.2 ^{1}H-NMR

^{1}H-NMR spectra of PMMA microspheres is given in Figure 4.3. The peak seen at 3.5 ppm is due to methoxy hydrogens (-OCH_3) and the peaks between 0.7 ppm

and 2.1 ppm are due to methyl hydrogens ($-CH_3$) and methylene ($-CH_2$) hydrogens. The peak at 7.2 ppm is due to deuterated chloroform ($CDCl_3$).

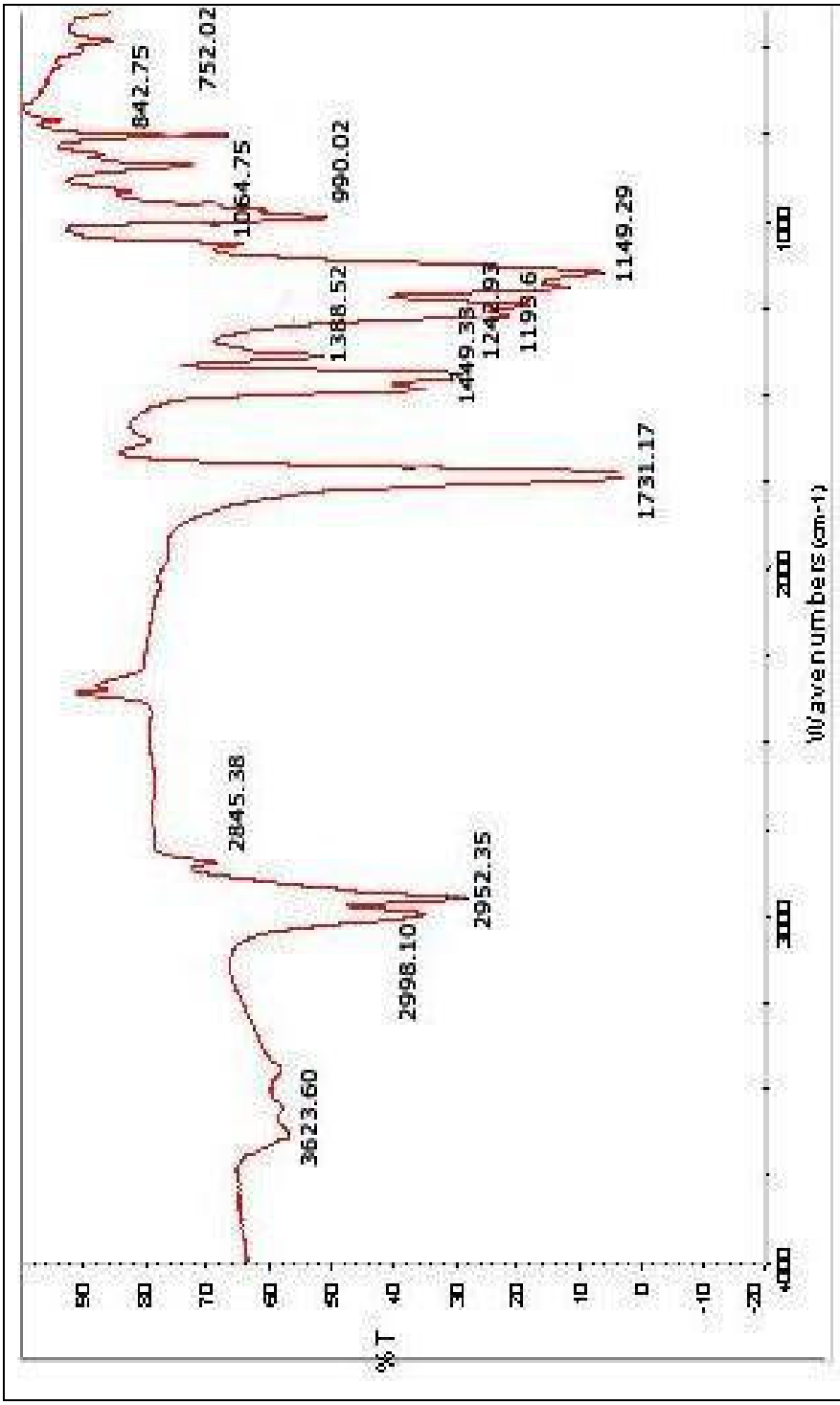

Figure 4.1 FTIR spectra of PMMA microspheres

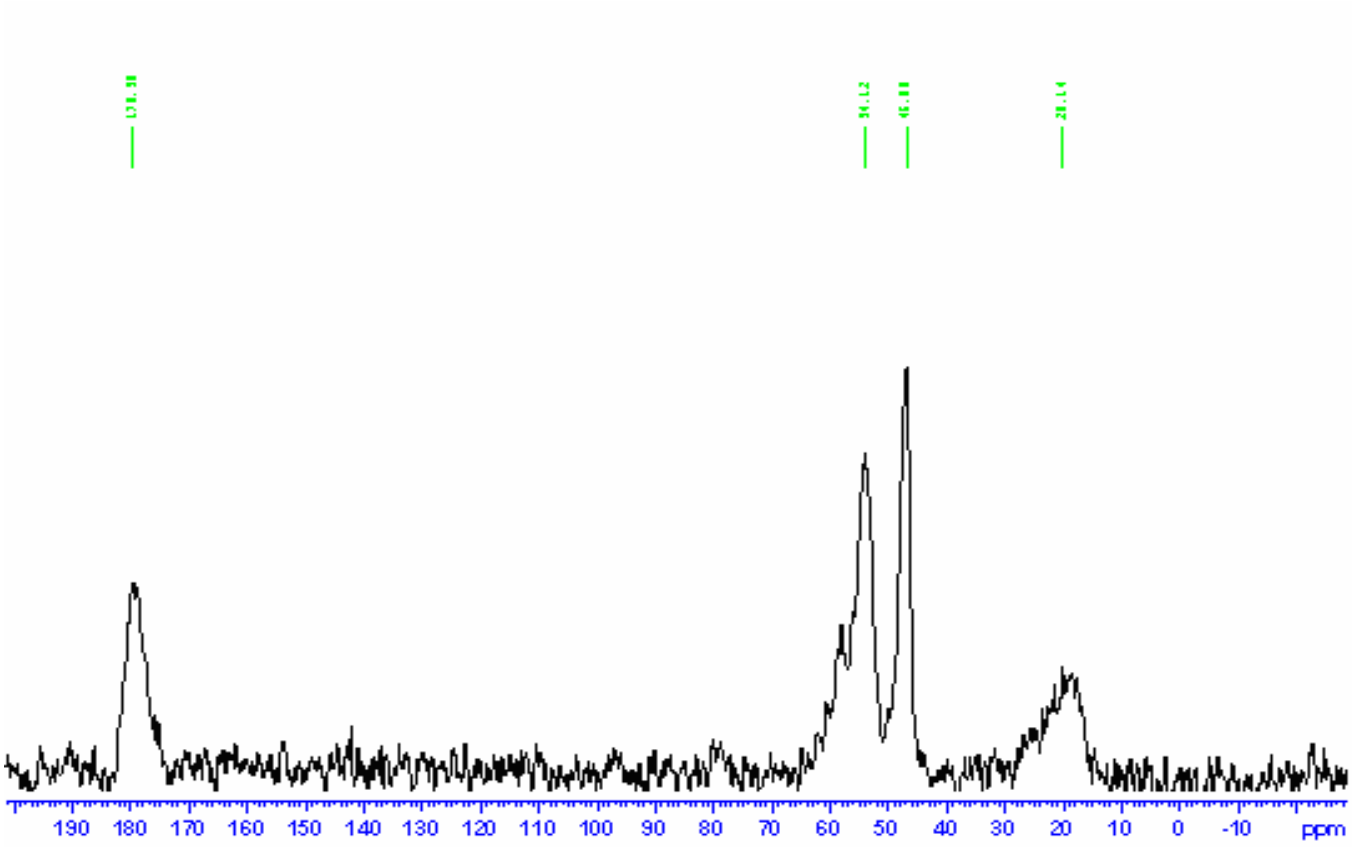

Figure 4.2 ^{13}C-NMR spectra of PMMA microspheres

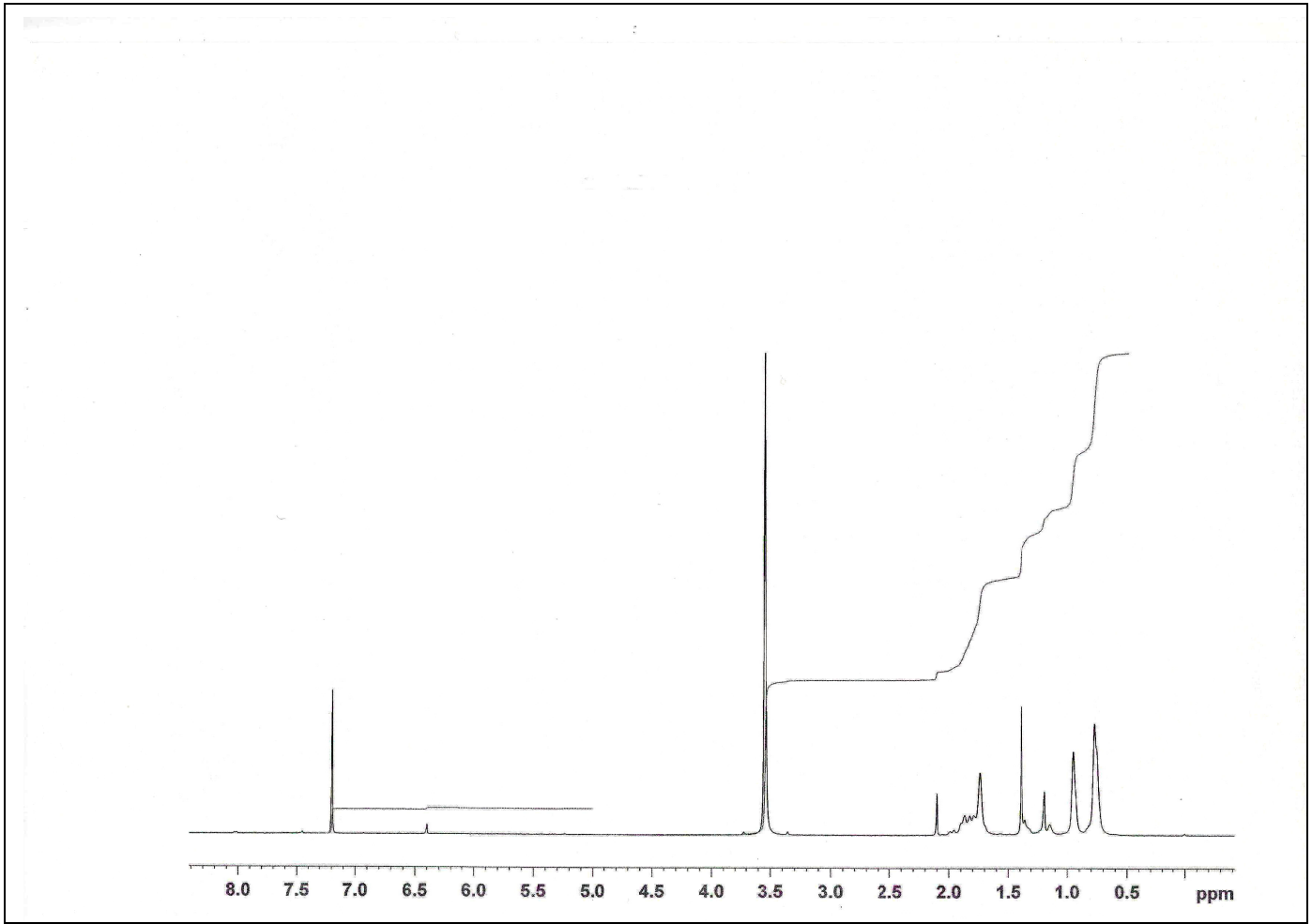

Figure 4.3 ^{1}H-NMR spectra of PMMA microspheres

4.3 SEM Analysis

Scanning electron micrographs of the PMMA microspheres are shown in Figure 4.4. The average particle size of PMMA microspheres is approximately 1 μm. It was observed that, particles are very homogenous and monodisperse with perfect spherical shape. These small size particles which were prepared by suspension polymerization were used in this study. The particle size of PMMA microspheres can be controlled by changing the polymerization parameters such as; temperature, initiator concentration, monomer concentration, molecular weight and concentration of stabilizer.

Since the average sizes of particles were about 1 μm, precise size distribution curves could not be obtained by Malvern Instrument. Therefore, particle size of PMMA microspheres was measured from SEM micrographs and by using Zeta Potential Analysis.

4.4 Particle Size Analysis

4.4.1 Particle size of PMMA microspheres

The particle size of PMMA microspheres was examined by Zeta Sizer. During the experiments distilled water was used as a dispersant and average particle size was found to be 1.01 μm. The size distribution is given in Figure 4.5. Particle size of the approximately 25% of the particles are below 1 μm.

4.4.2 Particle sizes of HA and $BaSO_4$ particles

The particle sizes of HA and $BaSO_4$ particles used in these experiments were detected by using MalvernTM Mastersizer (Malvern Instruments Ltd, UK). During the experiments distilled water was used as dispersant for both HA and $BaSO_4$ particles.

Average diameters (volume mean diameter) of the HA and $BaSO_4$ were found to be 23.63 μm and 6.72 μm, respectively. Particle size ranged from 0.5 to 112 μm for HA. The total volume of HA particles with diameters in the range of 15-30 μm represented 24.96% of the total volume of all HA particles in the distribution. 2.72% of the particles were in the nanosize range (<1 μm), 41.74% were in the 1-10 μm range and 46.40% of the particles were 10-50 μm range and 6.45% were in the 50-112 μm range. For $BaSO_4$, particle size ranged from 0.5 to 40

μm. 6.5% of the particles were in the nanosize range (<1 μm), 78.12% were in the 1-10 μm range and 15.38% of the particles were above 10 μm. The total volume of $BaSO_4$ particles with diameters of 5-10 μm represented 45.02% of the total volume of all $BaSO_4$ particles in the distribution. The particle size distribution of HA and $BaSO_4$ are given in Figure 4.6 and Figure 4.7, respectively.

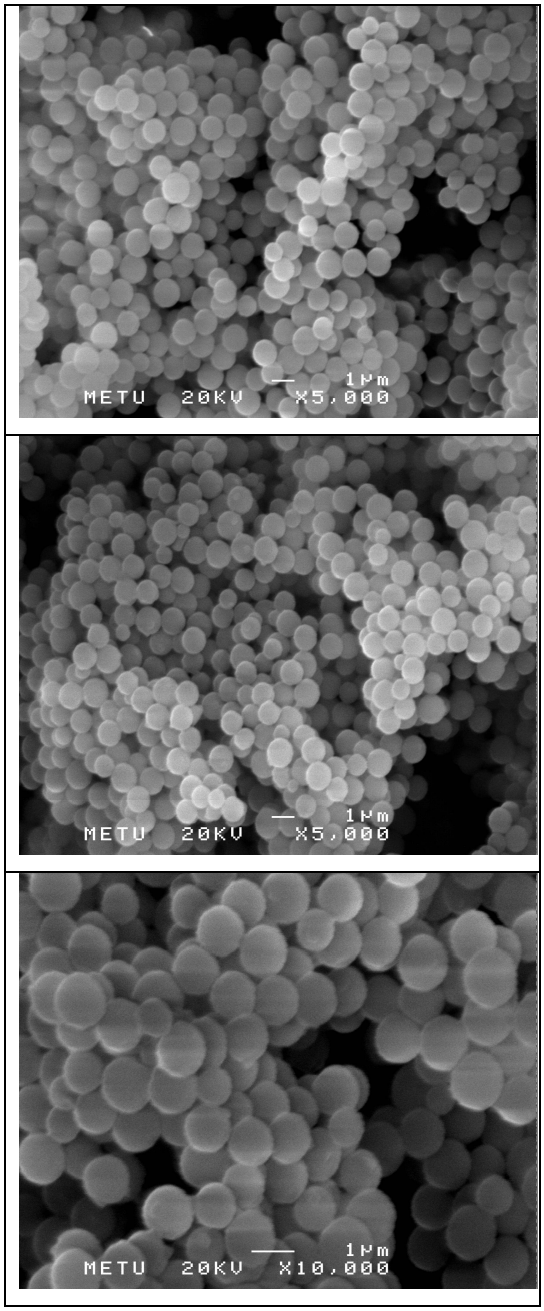

Figure 4.4 Scanning electron micrographs of PMMA microspheres

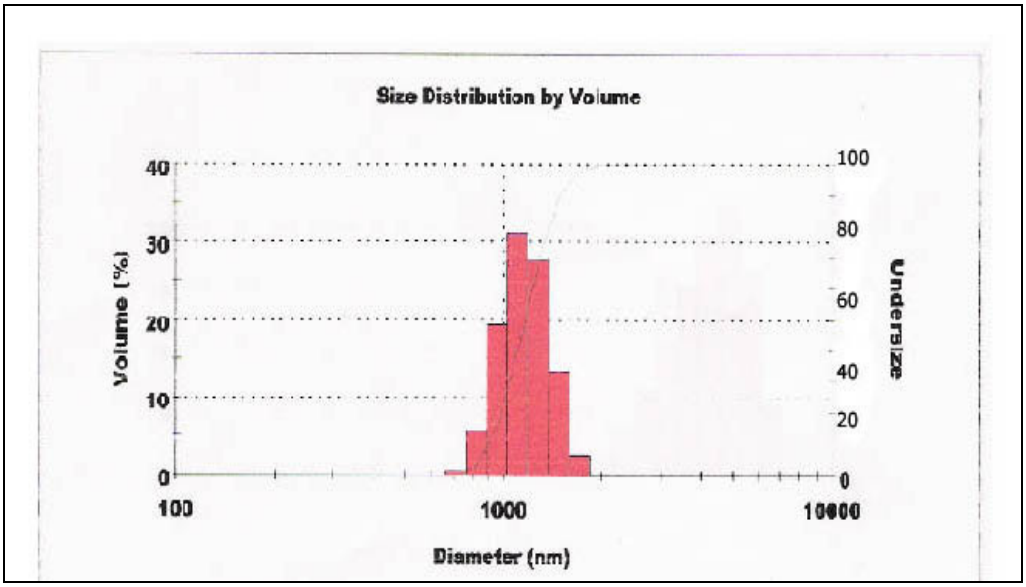

Figure 4.5 Particle size distribution of PMMA microspheres

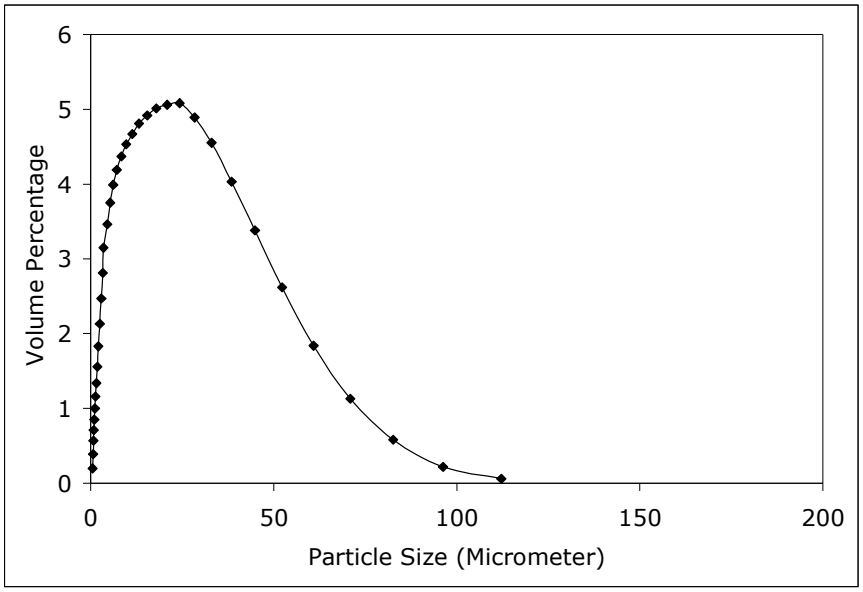

Figure 4.6 Particle size distribution of HA particles

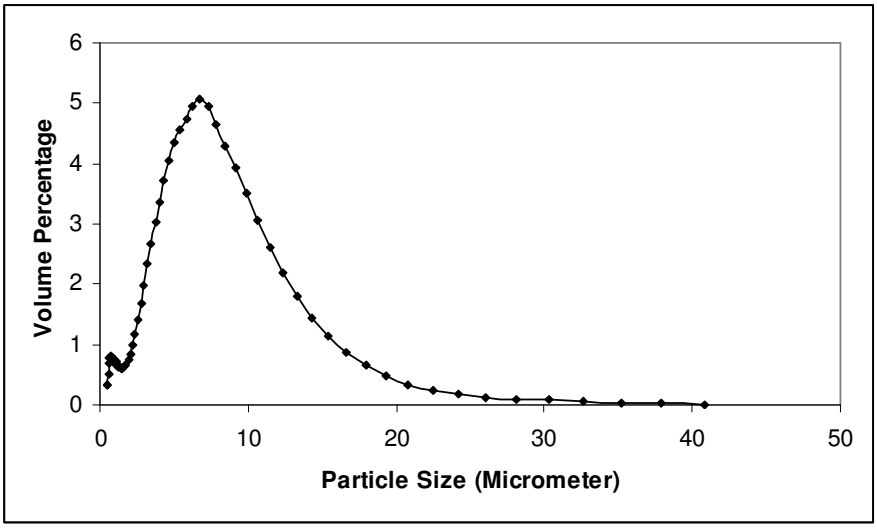

Figure 4.7 Particle size distribution of $BaSO_4$ particles

4.5 Mechanical Properties

For the prepared samples both tension and compression tests were applied.

4.5.1 Tension Tests

The average ultimate tensile strength (UTS) and elastic modulus (E_T) of the prepared bone cements were calculated from the graphs obtained for tension tests. For the samples prepared as control (BC1) without adding any ingredient, the UTS and E_T values were found as 20.40 MPa and 0.46 GPa, respectively.

Addition of HA caused an increase in UTS and it was found as 25.20 MPa when HA content was 8% (Table 4.1 and Figure 4.8). Addition of HA also caused an increase in elastic modulus. For the samples prepared with 8% HA addition, E_T value was found as 0.49 GPa (Table 4.1 and Figure 4.9). Although it is not very significant, the increase in tensile strength and elastic modulus can be explained as follows; HA has a stiffer structure in the polymeric matrix and therefore presence of these inorganic particles cause higher tensile strength and elastic modulus compared to cements prepared from PMMA without having any HA.

Table 4.1 Tensile properties of HA containing bone cement samples

Samples	HA wt%	UTS (MPa)	E_T (GPa)
BC1	0	20.40 ± 2.53	0.46 ± 0.04
BC2	4	24.87 ± 3.14	0.47 ± 0.03
BC3	8	25.20 ± 2.34	0.49 ± 0.01

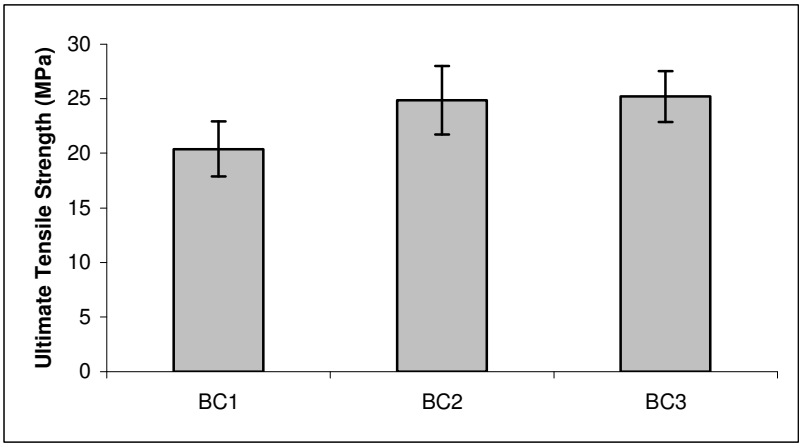

Figure 4.8 Ultimate tensile strength values of HA containing bone cements

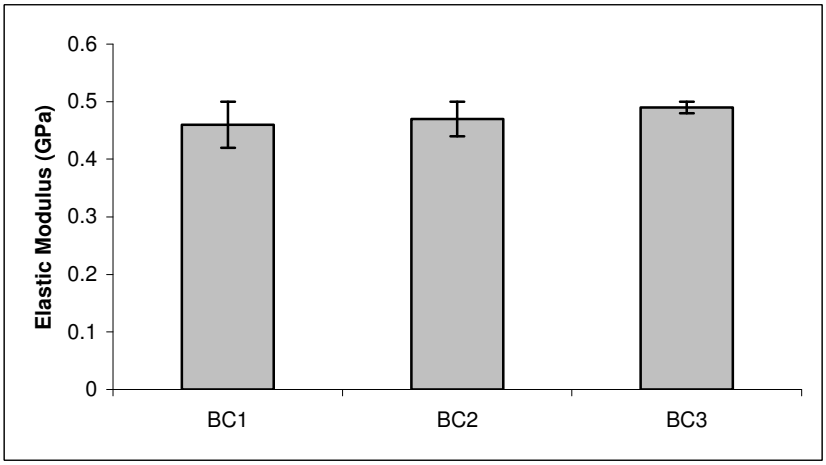

Figure 4.9 Elastic Modulus values of HA containing bone cements

Effect of $BaSO_4$ on mechanical properties was examined and it was observed that presence of $BaSO_4$ causes a decrease in both UTS and E_T (Table 4.2). When BC1 and BC4 samples are compared, $BaSO_4$ addition into the bone cement caused a small decrease in tensile strength and approximately 10.87% decrease in tensile elastic modulus from 0.46 GPa to 0.41 GPa. When HA containing samples, BC3 and BC5, are compared, again decreases in UTS value from 25.20 MPa to 20.64 MPa, and in E_T value from 0.49 GPa to 0.44 GPa were observed. These decreases are expected since radiopaque materials have significant effects on the mechanical properties of bone cements depending on their size and morphology. It was reported that small barium sulphate particles tended to form agglomerates and led to a decrease in tensile properties. Also barium sulphate particles didn't bond to the polymer matrix and did not provide mechanical anchorage. Therefore; a reduction in tensile properties were observed [51].

Table 4.2 Effect of $BaSO_4$ on tensile properties

Samples	HA (%)	$BaSO_4$ (%)	UTS (MPa)	E_T (GPa)
BC1	-	-	20.40 ± 2.53	0.46 ± 0.04
BC3	8	-	25.20 ± 2.34	0.49 ± 0.01
BC4	-	13	20.20 ± 2.43	0.41 ± 0.02
BC5	8	13	20.64 ± 2.47	0.44 ± 0.03

Chain transfer agent, 1-dodecyl mercaptan, also has effects on mechanical properties since its presence cause a decrease in chain lengths of PMMA chains in the matrix. DDM also controls the curing temperature of bone cement. Mechanical properties of DDM containing cements were examined and given in Table 4.3. The effect of DDM on ultimate tensile strength and elastic modulus of the prepared bone cements are given in Figures 4.10 and 4.11. Addition of 1% (BC6), 2% (BC7) and 3% (BC8) of 1-dodecyl mercaptan decreased the tensile strength down to 18.25 MPa, 17.84 MPa and 15.28 MPa, respectively. DDM controls the polymerization reaction and prevents formation of long chains and high molecular weight polymers. This fact may lead to a decrease in tensile properties of bone cements. BC6 bone cement containing 1% 1-dodecyl mercaptan demonstrated the maximum tensile elastic modulus (0.56 GPa) among all the prepared bone cements.

Table 4.3 Tensile properties of DDM containing bone cement samples

Samples	DDM wt%	UTS (MPa)	E_T (GPa)
BC5	0	20.64 ± 2.47	0.44 ± 0.03
BC6	1	18.25 ± 1.33	0.56 ± 0.05
BC7	2	17.84 ± 1.77	0.40 ± 0.02
BC8	3	15.28 ± 0.56	0.39 ± 0.05

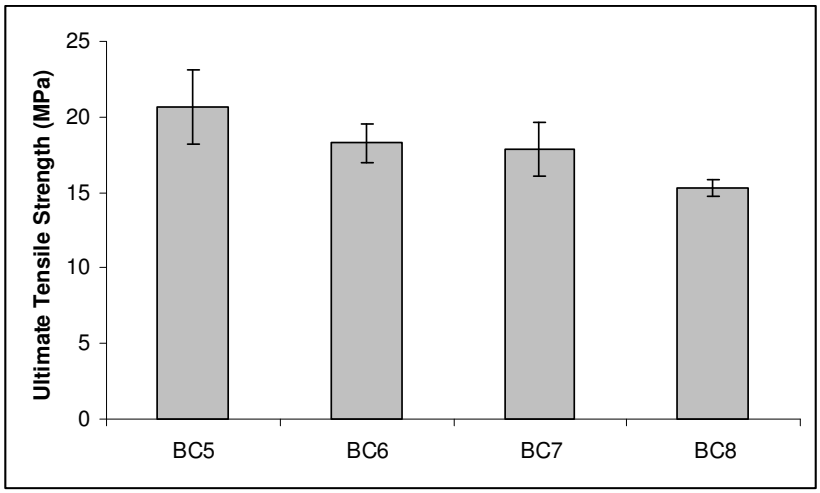

Figure 4.10 Ultimate tensile strength values of DDM containing bone cements

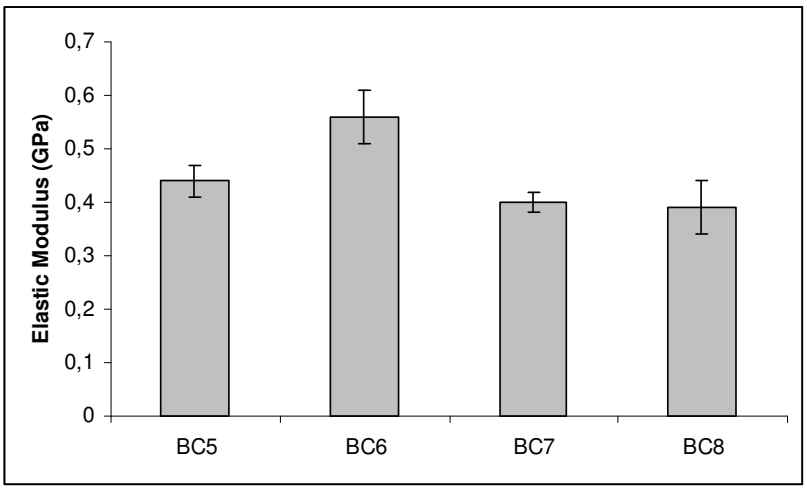

Figure 4.11 Elastic Modulus of values of DDM containing bone cements

The mechanical properties of commercially available bone cement CEMEX were also examined. It was observed that tensile strength and elastic modulus of CEMEX was 23.84 MPa and 0.48 GPa, respectively. The tensile properties of all bone cement samples are given in Table 4.4 and Figures 4.12, 4.13.

Table 4.4 Tensile properties of prepared bone cement samples

Samples	UTS (MPa)	E_T (GPa)
BC1	20.40 ± 2.53	0.46 ± 0.04
BC2	24.87 ± 3.14	0.47 ± 0.03
BC3	25.20 ± 2.34	0.49 ± 0.01
BC4	20.20 ± 2.43	0.41 ± 0.02
BC5	20.64 ± 2.47	0.44 ± 0.03
BC6	18.25 ± 1.33	0.56 ± 0.05
BC7	17.84 ± 1.77	0.40 ± 0.02
BC8	15.28 ± 0.56	0.39 ± 0.05
CEMEX	23.84 ± 3.75	0.48 ± 0.04

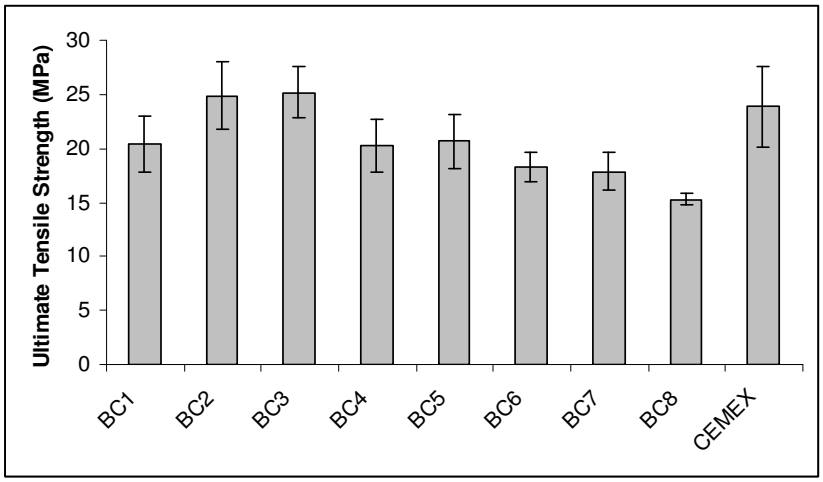

Figure 4.12 Ultimate tensile strength values of the prepared bone cements

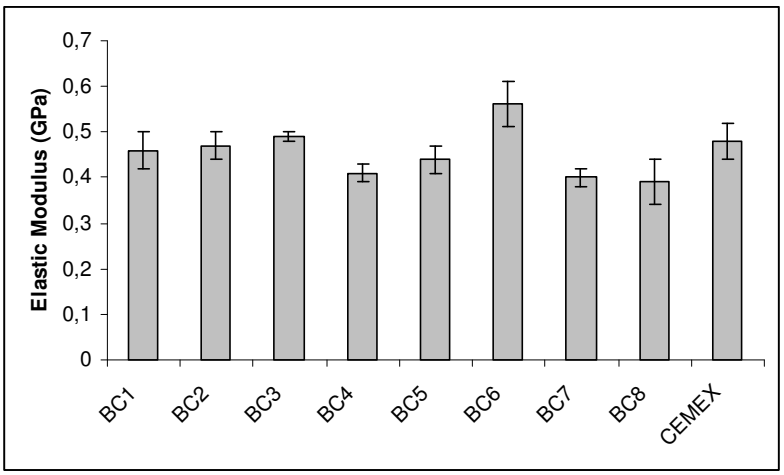

Figure 4.13 Elastic modulus values of the prepared bone cements

4.5.2 Compression Tests

The average ultimate compressive strength (UCS) and elastic modulus (E_C) values of the prepared bone cements were calculated. It was observed that all prepared bone cements fulfilled the minimum compressive strength (70 MPa) requirement specified by ASTM F-451.

Addition of HA up to 8% increased the ultimate compressive strength from 84.04 MPa to 89.57 MPa (Table 4.5, Figures 4.14 and 4.15). In addition; elastic modulus of the cement was also increased with HA addition from 0.54 GPa to 0.59 GPa (Table 4.5 and Figure 4.16). These increases are expected since HA particles act as load carrier component against compressive forces.

Table 4.5 Compressive properties of HA containing bone cement samples

Samples	HA wt%	UCS (MPa)	E_C (MPa)
BC1	0	84.04 ± 2.91	0.54 ± 0.03
BC2	4	87.77 ± 1.86	0.57 ±0.03
BC3	8	89.57 ± 2.44	0.59 ± 0.03

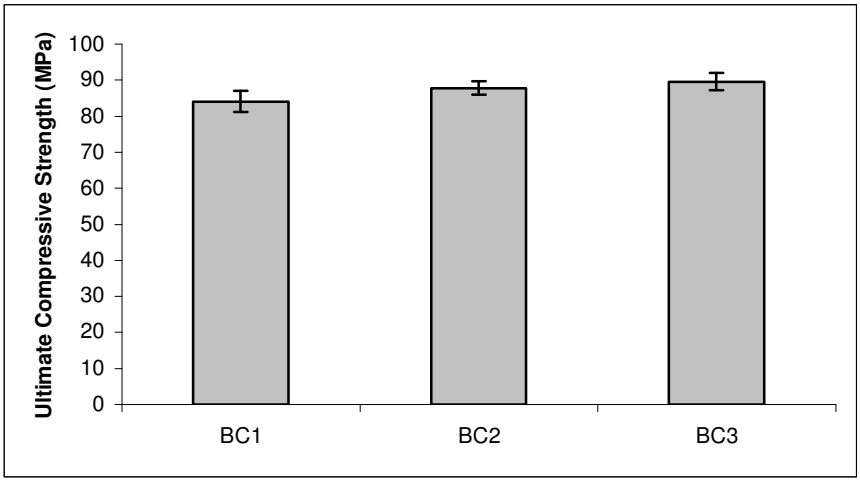

Figure 4.14 Ultimate compressive strength values of HA containing bone cements

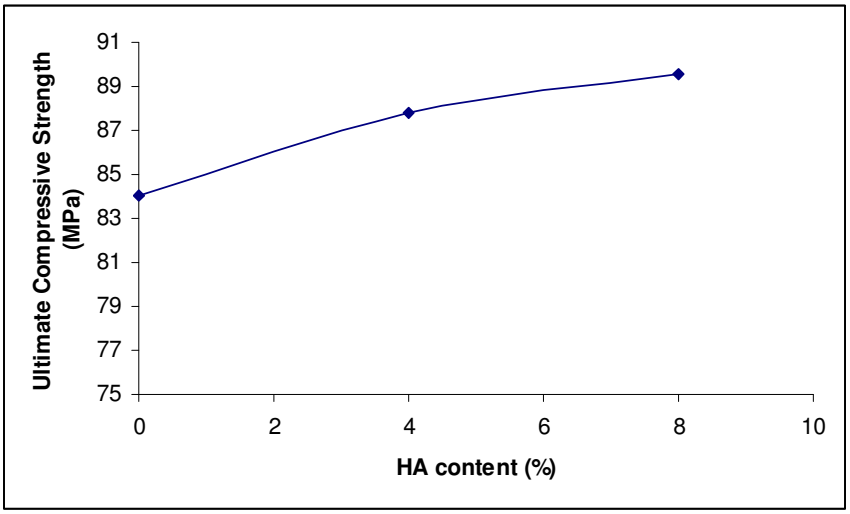

Figure 4.15 Change in ultimate compressive strengths of 0%, 4%, 8% HA containing bone cements

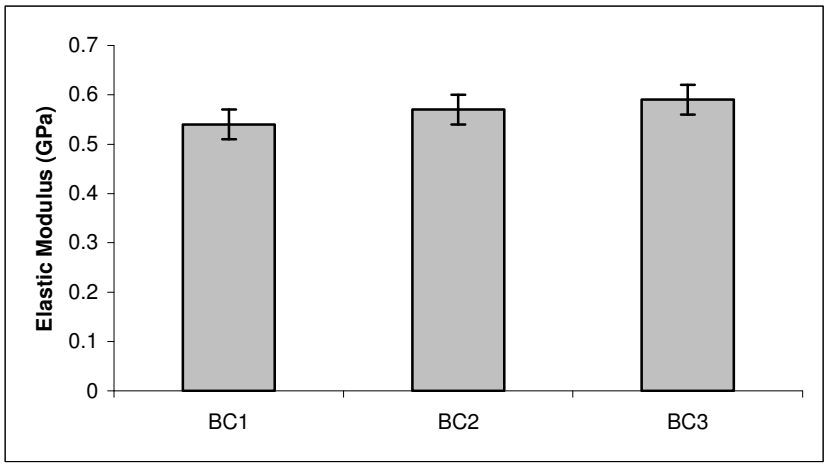

Figure 4.16 Elastic modulus values of HA containing bone cements

Effect of $BaSO_4$ addition on compressive properties of the samples is given in Table 4.6. When BC1 and BC4 samples are compared it can be observed that ultimate compressive strength decreased from 84.04 MPa to 80.35 MPa and compressive elastic modulus increased from 0.54 GPa to 0.57 GPa with the addition of 13% $BaSO_4$.

The similar effects were also observed for HA containing samples. When BC3 and BC5 samples are compared, a decrease in UCS from 89.57 MPa to 78.83 MPa can be observed. For these samples, no change in E_C values was detected.

Table 4.6 Compressive properties of $BaSO_4$ containing bone cement samples

Samples	HA (%)	$BaSO_4$ (%)	UCS (MPa)	E_C (MPa)
BC1	-	-	84.04 ± 2.91	0.54 ± 0.03
BC3	8	-	89.57 ± 2.44	0.59 ± 0.03
BC4	-	13	80.35 ± 1.71	0.57 ± 0.02
BC5	8	13	78.83 ± 1.75	0.59 ± 0.01

The compressive properties of bone cements prepared with the addition of DDM are given in Table 4.7. The effect of DDM addition on the compressive properties is also shown in Figures 4.17 and 4.18. The ultimate compressive strength value of BC6 samples (containing 1% DDM) was found as 86.90 MPa and increased to

93.01 MPa (BC7) when 2% 1-dodecyl mercaptan was added. However then further addition of DDM decreased the UCS to 82.16 MPa (BC8). Compressive elastic modulus was also increased from 0.59 GPa to 0.62 GPa with addition of 1% DDM, but further additions caused a drop in E_C value.

Table 4.7 Compressive properties of DDM containing bone cement samples

Samples	DDM (wt%)	UCS (MPa)	E_C (GPa)
BC5	0	78.83 ± 1.75	0.59 ± 0.01
BC6	1	86.90 ± 4.50	0.62 ± 0.02
BC7	2	93.01 ± 3.59	0.59 ± 0.01
BC8	3	82.16 ± 3.78	0.58 ± 0.06

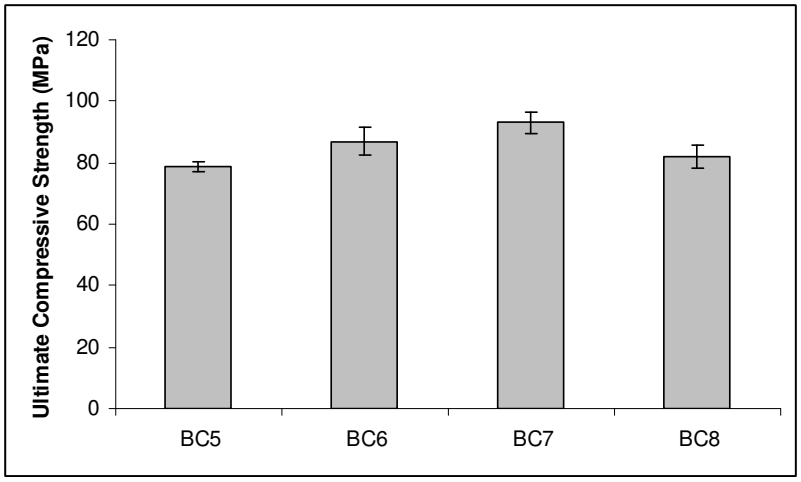

Figure 4.17 Ultimate Compressive Strength values of DDM containing bone cements

These results are expected since DDM gives some softness to the hard PMMA matrix and therefore increase the strength against higher compression forces. But further additions may cause very short chains and cause a drop in compressive strength values.

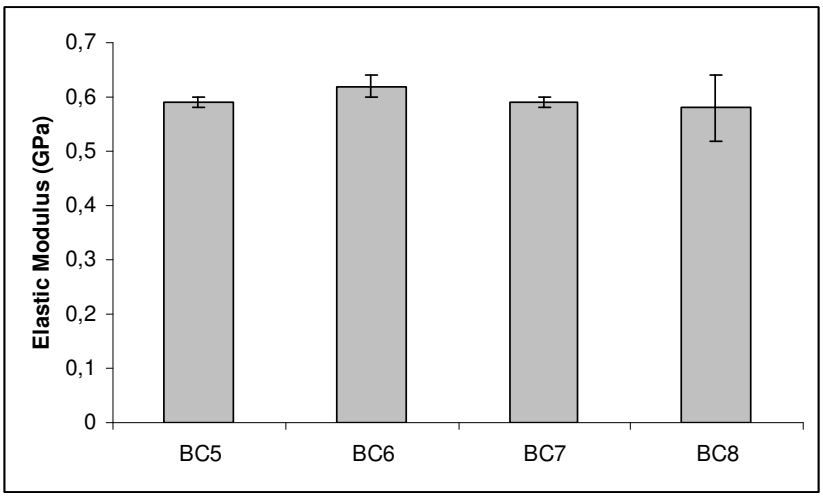

Figure 4.18 Elastic Modulus of values of DDM containing bone cements

Compressive properties of all samples prepared in this study are given in Table 4.8 and Figure 4.19 and 4.20.

Table 4.8 Compressive properties of bone cement samples

Samples	**UCS (MPa)**	**E_C (GPa)**
BC1	84.04 ± 2.91	0.54 ± 0.03
BC2	87.77 ± 1.86	0.57 ±0.03
BC3	89.57 ± 2.44	0.59 ± 0.03
BC4	80.35 ± 1.71	0.57 ± 0.02
BC5	78.83 ± 1.75	0.59 ± 0.01
BC6	86.90 ± 4.50	0.62 ± 0.02
BC7	93.01 ± 3.59	0.59 ± 0.01
BC8	82.16 ± 3.78	0.58 ± 0.06
CEMEX	101.06 ± 2.05	0.49 ± 0.04

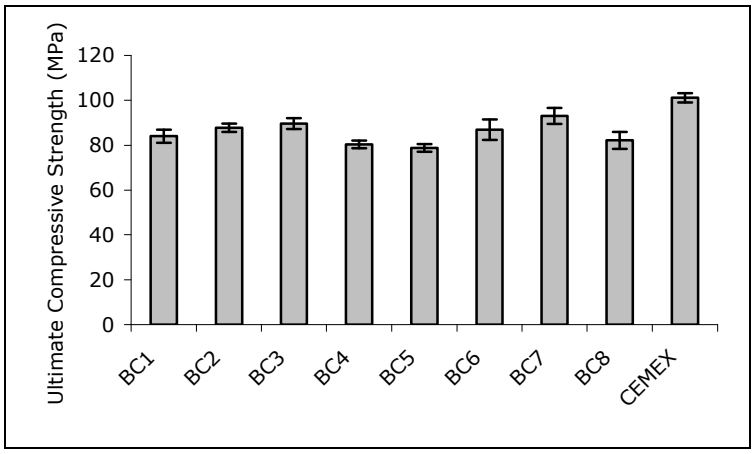

Figure 4.19 Ultimate compressive strength values of prepared bone cements

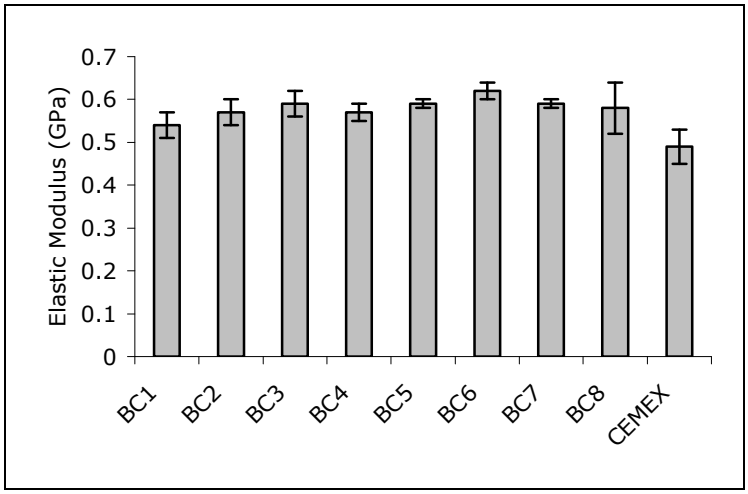

Figure 4.20 Elastic modulus values of prepared bone cements

4.6 Curing Temperature

The polymerization of MMA-PMMA system is highly exothermic and leads to an increase in local temperature. This increase in temperature is dependent on MMA-PMMA ratio, the composition of liquid and solid components, the concentration of initiator and accelerator, presence of chain transfer agent and particle size of the PMMA. It was stated in literature that PMMA particles larger than 50-60 μm could absorb the produced heat during the setting process and smaller than 20 μm undergo complete dissolution in the polymerizing MMA medium therefore it may cause an increase in the viscosity and curing temperature of the cement [12]. In this study PMMA microspheres with

approximately 1 μm size were used and curing temperatures were found to be in the range of 71 -101ºC. During the temperature measurements bone cement dough was rounded to give a spherical shape and the curing temperature was recorded by using J-type thermocouples. It was noted that placing the thermocouple at the center of the cement dough was quick, simple and reproducible however the temperature values obtained in this way were not clinically important temperatures, since a sphere has a small surface to volume ratio and provides relatively low heat dissipation [31]. Therefore the values obtained in this way are higher than the clinically applied thin layer cements. But in this study, in order to have a proper comparison between the samples, spherical dough shapes were preferred and used.

Usually commercial bone cements have a polymer-to-monomer ratio of 2. But in this study the average particle size of the synthesized PMMA microspheres was about 1 μm and the surface to volume ratio of these small microspheres was much higher than 50-60 μm particles. Hence, the amount of monomer used in the given ratio was not enough to wet all powder particles when polymer-to-monomer ratio was kept as 2. Therefore, powder to monomer ratio was decreased to 0.7. It is known that the maximum temperature reached during polymerization increases with decreasing polymer-to-monomer ratio. Therefore, maximum temperatures occurred during setting processes were measured. Maximum temperatures and setting times of the HA and $BaSO_4$ containing bone cements are given in Table 4.9. The maximum temperature of BC1 sample containing 0% HA was 101.78ºC and decreased to 98.52ºC and 97.97ºC when 4% and 8% HA was added, respectively. HA acted as a heat sink and caused a reduction in temperature although the difference between BC2 and BC3 samples were not significant. Addition of $BaSO_4$ (BC4) did not cause a noticeable difference when BC1 and BC4 samples and when BC3 and BC5 samples were compared. The temperature difference was very small. On the other hand, although $BaSO_4$ addition has not a significant difference in temperature change, it can be concluded that by addition of HA, the maximum temperature can be decreased by 5ºC.

Addition of 1%, 2% and 3% DDM chain stopping agent, relative to the amount of MMA monomer, decreased the maximum temperature from 96.83ºC to 91.80°C, 78.38°C and 71.35°C, respectively as shown in Table 4.10. Chain stopping agent

controls the polymerization reaction and prevents the highly exothermic reaction. Therefore, these decreases are expected.

Table 4.9 Thermal properties of bone cement samples

Samples	HA (%)	$BaSO_4$ (%)	Thermal Properties	
			T_{max} (°C)	$t_{setting}$ (sec)
BC1	-	-	101.78 ± 0.20	409 ± 35
BC2	4	-	98.52 ± 4.24	362 ± 31
BC3	8	-	97.97 ± 3.55	327 ± 14
BC4	-	13	102.24 ± 3.45	356 ± 9
BC5	8	13	96.83 ± 7.56	361 ± 26

Table 4.10 Thermal properties of DDM containing bone cement samples

Samples	DDM (%)	Thermal Properties	
		T_{max} (°C)	$t_{setting}$ (sec)
BC5	-	96.83 ± 7.56	361 ± 26
BC6	1	91.8 ± 0.11	434 ± 4
BC7	2	78.38 ± 2.46	472 ± 3
BC8	3	71.35 ± 3.69	550 ± 48

The curing temperature and the setting time of CEMEX bone cement were found to be 82.12°C and 868 seconds, respectively. The curing temperatures of all prepared bone cements are given in Table 4.11 and Figure 4.21. As it can be seen, BC7 and BC8 samples demonstrated lower curing temperatures compared to commercially available CEMEX cement.

Table 4.11 Thermal properties of prepared bone cement samples

Samples	Thermal Properties	
	T_{max} (°C)	$t_{setting}$ (sec)
BC1	101.78 ± 0.20	409 ± 35
BC2	98.52 ± 4.24	362 ± 31
BC3	97.97 ± 3.55	327 ± 14
BC4	102.24 ± 3.45	356 ± 9
BC5	96.83 ± 7.56	361 ± 26
BC6	91.80 ± 0.11	434 ± 4
BC7	78.38 ± 2.46	472 ± 3
BC8	71.35 ± 3.69	550 ± 48
CEMEX	82.12 ± 2.54	868 ± 12

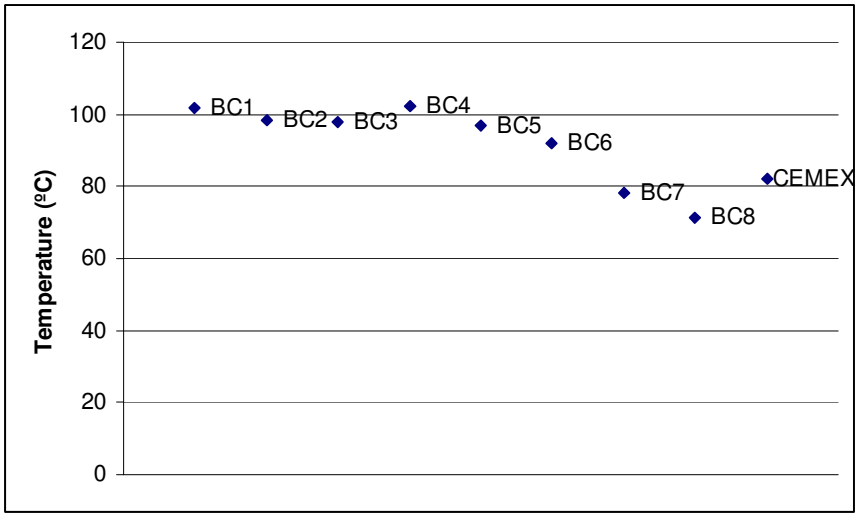

Figure 4.21 Change in curing temperatures of prepared bone cements

4.7 Scanning Electron Microscopy Results

Acrylic bone cements are prepared by mixing powder and liquid parts, during mixing air bubbles may be entrapped in the cement and lead to formation of pores. Porosity is one of the factors that decrease the mechanical strength of the

cement. In addition; exothermic polymerization reaction may also cause fast evaporation of MMA monomer and as a consequence lead to porosity. Pores can be seen in the SEM photos. When BC1 sample prepared without HA and BC3 sample containing 8% HA were compared, it was observed that pore size was decreased with the addition of HA (Figure 4.22). HA acted as a heat sink, absorbed produced heat and lead to a decrease in curing temperature decreasing evaporation of MMA, therefore the pore sizes were reduced.

Particle size of the HA was 23.63 μm, considerably large when compared to PMMA microspheres and $BaSO_4$ particles. In SEM micrographs white HA particles are distinguishable at the fracture surfaces.

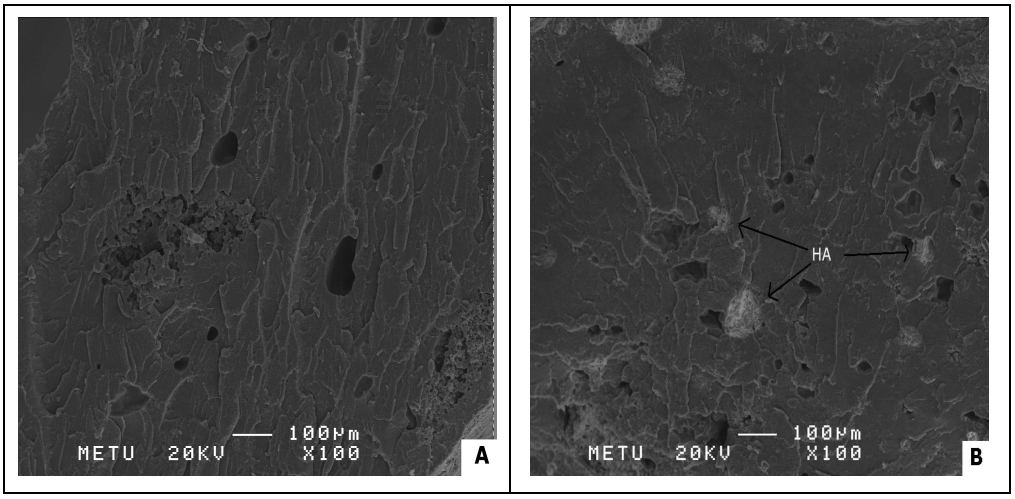

Figure 4.22 Pore distribution of bone cements A) without HA (BC1) and B) with 8% HA (BC3)

It was observed that addition of DDM reduced the pore size of the samples. DDM as a chain stopping agent, controlled the polymerization reaction and prevented the highly exothermic reaction, therefore fast evaporation of MMA monomer was reduced (Figure 4.23).

From the SEM micrographs it can also be observed that, PMMA microspheres were not completely dissolved in the freshly formed matrix. The existence of microspheres may also create phase segregation which may demonstrate its effect in both directions on mechanical properties. Up to a certain value, microspheres may demonstrate an increase in mechanical properties behaving

as shock absorbers. But further amounts may cause weakness creating incompatibility. It is also interesting that, high decrease in polymer-to-monomer ratio from 2 to 0.7 still did not achieve a complete wetting for microspheres. This part needs extra studies.

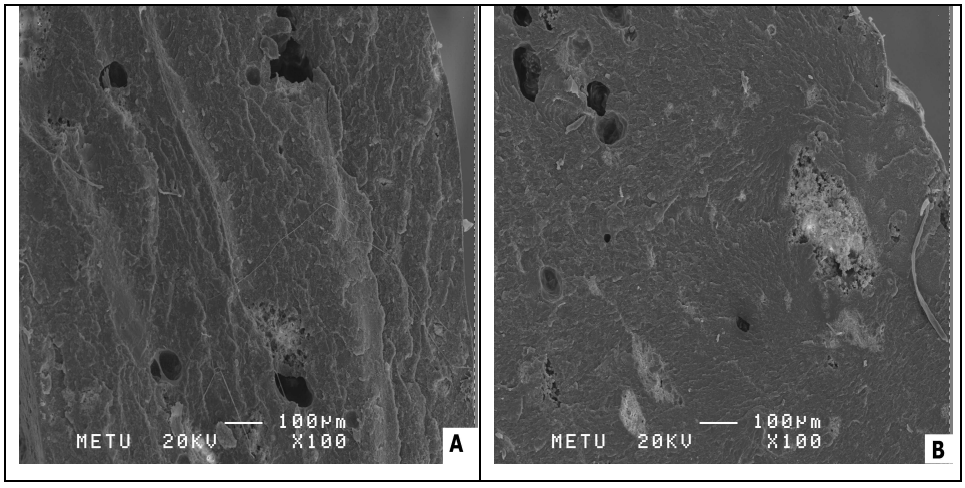

Figure 4.23 Pore distribution of bone cements A) with 1% DDM (BC6) and B) with 3% DDM (BC7)

CHAPTER 5

CONCLUSIONS

Bone cements must have good mechanical properties to endure cyclic loads applied during daily activities, must have low curing temperature in order not to damage the environmental tissue and they must be biocompatible.

In this study various bone cement formulations were prepared by using poly(methyl methacrylate) (PMMA) microspheres which were prepared by suspension polymerization, barium sulphate ($BaSO_4$) radiopaque agent, hydroxyapatite (HA) particles and 1-dodecyl mercaptan (DDM) chain stopping agent. Mechanical and thermal properties of the prepared bone cements were examined and all results obtained in this study are summarized in Table 5.1 and Table 5.2.

Previously it was reported that HA addition increased the biocompatibility of the bone cement [62], and also it was observed that presence of HA increased both tensile and compressive strengths. Ultimate compressive strength values increased from 84.04 MPa to 89.57 MPa and ultimate tensile strength values increased from 20.40 MPa to 25.20 MPa with addition of 8% HA. Moreover; HA addition reduced curing temperature since it achieved a heat sink property by absorbing the released heat. The maximum temperature of the sample containing 0% HA was 101.78ºC and decreased to 97.97ºC with addition of 8% HA.

$BaSO_4$ was added to provide radiopacity since it is essential to monitor cement after surgery. Radiopaque materials have significant effects on the mechanical properties of bone cements depending on their size and morphology. It was observed that addition of 13% $BaSO_4$ led to a reduction in both compressive and tensile strength without a significant change in curing temperature.

Table 5.1 Mechanical properties of prepared bone cement samples

Samples	Tensile Properties		Compressive Properties	
	UTS (MPa)	E_T (GPa)	UCS (MPa)	E_C (GPa)
BC1	20.40 ± 2.53	0.46 ± 0.04	84.04 ± 2.91	0.54 ± 0.03
BC2	24.87 ± 3.14	0.47 ± 0.03	87.77 ± 1.86	0.57 ±0.03
BC3	25.20 ± 2.34	0.49 ± 0.01	89.57 ± 2.44	0.59 ± 0.03
BC4	20.20 ± 2.43	0.41 ± 0.02	80.35 ± 1.71	0.57 ± 0.02
BC5	20.64 ± 2.47	0.44 ± 0.03	78.83 ± 1.75	0.59 ± 0.01
BC6	18.25 ± 1.33	0.56 ± 0.05	86.90 ± 4.50	0.62 ± 0.02
BC7	17.84 ± 1.77	0.40 ± 0.02	93.01 ± 3.59	0.59 ± 0.01
BC8	15.28 ± 0.56	0.39 ± 0.05	82.16 ± 3.78	0.58 ± 0.06
CEMEX	23.84 ± 3.75	0.48 ± 0.04	101.06 ± 2.05	0.49 ± 0.04

Table 5.2 Thermal properties of prepared bone cement samples

Samples	Thermal Properties	
	T_{max} (°C)	$t_{setting}$ (sec)
BC1	101.78 ± 0.20	409 ± 35
BC2	98.52 ± 4.24	362 ± 31
BC3	97.97 ± 3.55	327 ± 14
BC4	102.24 ± 3.45	356 ± 9
BC5	96.83 ± 7.56	361 ± 26
BC6	91.80 ± 0.11	434 ± 4
BC7	78.38 ± 2.46	472 ± 3
BC8	71.35 ± 3.69	550 ± 48
CEMEX	82.12 ± 2.54	868 ± 12

1-Dodecyl mercaptan chain stopping agent was added to decrease curing temperature of bone cement. Chain stopping agent controls the polymerization reaction and prevents the highly exothermic reaction. Relative to the amount of MMA, if 1%, 2% and 3% DDM chain stopping agent was added, the maximum curing temperature decreased from 101.78°C to 91.80°C, 78.38°C and 71.35°C,

respectively. However; addition of 1% (BC6), 2% (BC7) and 3% (BC8) 1-dodecyl mercaptan decreased the tensile strength down to 18.25 MPa, 17.84 MPa and 15.28 MPa, respectively.

Compressive strength values of all the prepared bone cements are in acceptable range and higher than the required 70 MPa value. Curing temperature of the bone cements was decreased with DDM addition.

Although tensile strengths of BC7 and BC8 samples are low, their compressive strength values are above the required minimum value and their curing temperatures are much lower than the commercial cement. Therefore, BC7 and BC8 can be good candidates as bone cements.

Further studies should be achieved in order to improve the mechanical and thermal properties of the acrylic bone cements. One suggestion can be the use of larger PMMA microspheres (~50 μm) to decrease the curing temperature and this can be adjusted by changing the parameters of suspension polymerization process. Another suggestion can be the use of copolymers of PMMA in order to increase their tensile strength values. Another parameter is the mixing process and vacuum mixing instead of hand mixing can be applied to decrease the amounts of pores. Of course the existence of large number of parameters makes the process complicate and optimization becomes difficult. But whatever the case it is also necessary to achieve in-vivo experiments with the cements in order to check their biocompatibilities although all the chemicals used in this study are also used in commercially available cement formulations.

If the bone cements with the desired properties could be produced, it would be a great gain for the country in both social and economical aspects.

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