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Radiopaque Polymeric Materials for Medical Applications : Current Aspects of Biomaterial Research

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Abstract

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ABSTRACT. The aim of this review is to give an overview and some insight into different radiopaque polymeric materials that are currently used as medical implants or inserts. The advantages and limitations of each radiopaque polymeric material are summarized. The main method used to make medical implants radiologically visible is based on blending polymers with conventional radiopaque agents, blends which usually are a physical mixture of acrylic derivatives and inorganic salts. Other methods reported involve either the formation of single-phase radiopaque polymer salt complexes somehow preventing the release of the radiopacifying element by entrapment of the complex in a crosslinked network, or radiopaque polymerized monomers characterized by a radiopacifying element associated with the monomer unit prior to polymerization. In the near future, research will certainly concentrate on biocompatible radiopaque polymers with covalently bound opaque elements leading to stable polymers with properties equivalent to the nonopaque, parent polymer.

DIAGNOSTIC contrast materials have to satisfy an extensive list of requirements to be safe and useful for analyses involving a temporary passage through the human body. However, these materials have to satisfy somewhat different criteria when used to render a medical implant visible.

Radiopacity of Implants

The radiological detectability of conventional polymers used as medical implants or inserts is limited by their density, which is similar to that of soft tissue due to their molecular structures containing the same elements such as hydrogen, oxygen, nitrogen, or carbon. In order to improve the radiological visibility, several methods have been developed to increase the density, i.e., the average electron density and the specific gravity of polymers, by incorporating heavy elements.

Early studies focused on the incorporation of heavy-metal salts as physical mixtures. A major problem of this method lies in the creation of nonhomogeneous mixtures, owing to the basic incompatibility between ionic salts and resins, which modify the mechanical properties of the products. To overcome this drawback, polymer-radiopaque salt complexes were developed exhibiting the characteristics of a single phase solution. These derivatives are obtained by the incorporation of heavy-metal salts into the polymer backbone via chelation without degradation of the intrinsic polymer characteristics.

Another more promising approach involved the introduction of radiopaque elements inside monomers prior to their polymerization. This method can prevent the secondary release of radiopacifying agent, which can otherwise leak out of the implant (Figure 1).

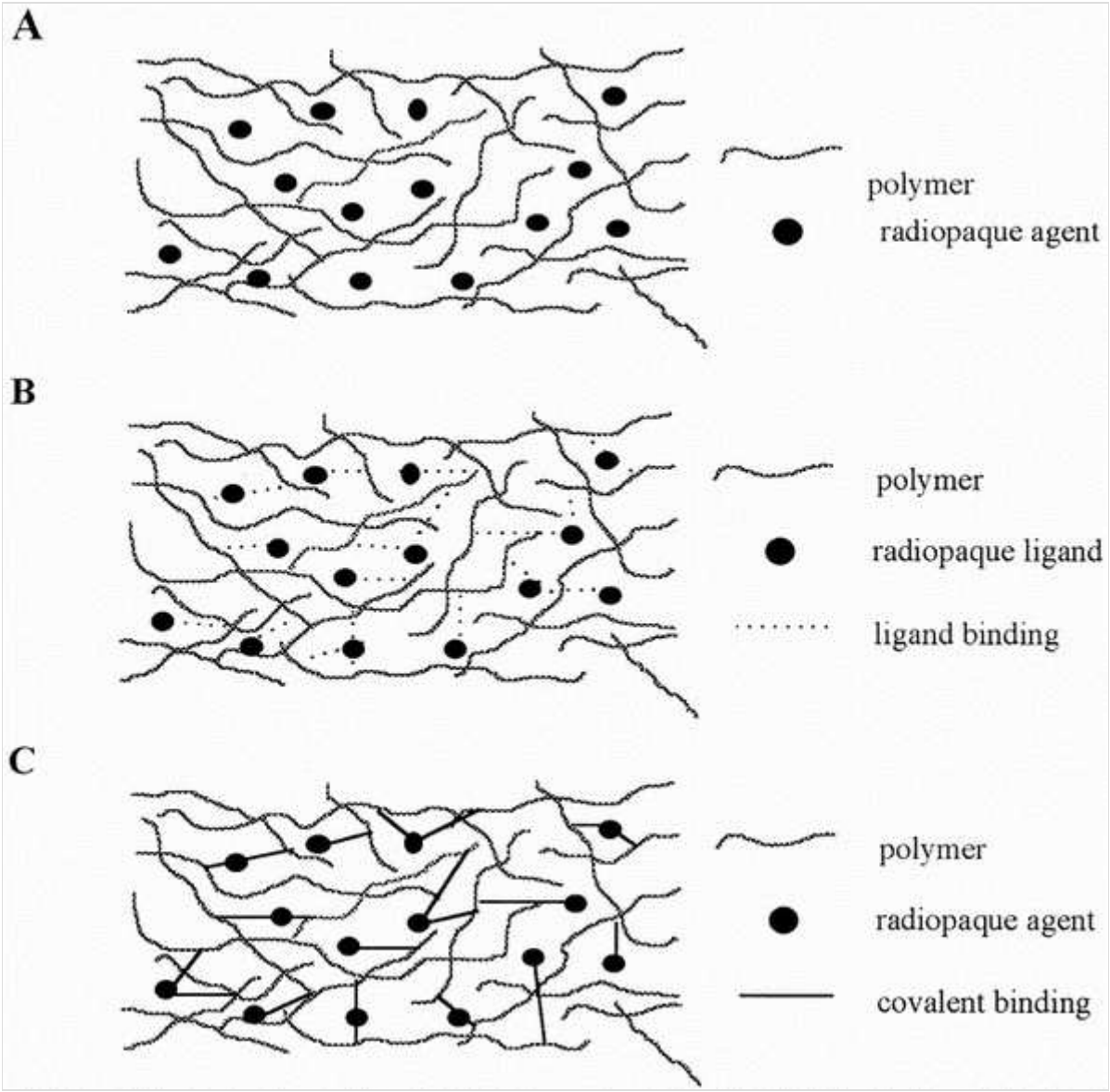

Figure 1. Radiopaque polymeric materials: (A) radiopaque polymer blends, (B) radiopaque polymer salt complexes, and (C) radiopaque polymerized monomers.

This paper reviews the different methods used to render an implantable polymer radiopaque during the implantation procedure. Some advantages and drawbacks of the different polymer classes are discussed, excluding, however, discussion of compatibility issues in regard to radiopacifying agents.

Polymerization Versus Precipitation

Polymers, also called macromolecules, are very large molecules made up of the repetition of some simpler units, the mers or monomers. The monomers are linked together by a process called polymerization, which can give rise to linear, branched, or crosslinked polymers. 1,2

Homopolymers consist of only one type of repeating unit, whereas copolymers are composed of two or more different monomer units arranged in either random or alternating sequences. In this paper, two different processes to implant polymeric materials are described. In a first case, monomers can be injected at the site of application and polymerized by an initiator, which is the technique described for acrylic monomers such as isobutyl 2-cyanoacrylate (IBCA) or methyl methacrylate (MMA). The major problems encountered with the monomers polymerizing in situ are the presence or possible release of toxic monomers, polymerization initiators, or solvents added to the reacting medium. 3-5

Another method described in the literature focuses on the precipitation of preformed polymers solubilized in an appropriate organic solvent. In this case, the polymer deposition depends on the phase separation of the solution in the presence of a nonsolvent such as physiological fluid, and the precipitation of the polymer. 1 Precipitating polymers described as polymeric implants are cellulose derivatives or ethylene vinyl alcohol copolymer (EVAL). Potential toxic effects described with these derivatives are mainly related to the diffusion of organic solvents into human tissue. It is worth noting that with preformed polymers no release of potentially toxic monomers occurs.

Radiopacity and Its Standards

As with light, x-rays are characterized by an electromagnetic vibration with a wavelength ranging from 12 to 0.06 A. Absorption occurs from the interaction of x-ray photons with electrons in the observed structure, promoting these electrons to higher energy levels at a rate proportional to the electron concentration, 6 and thus gives rise to the radiopacity observed on the x-ray film. Radiopaque elements are described by a relationship between their atomic number and their ability to absorb x-rays: 7,8 MATH where [mu] is the absorption coefficient, [lambda] the wavelength of the x-rays, Z the atomic number, and 0.2 the average coefficient of scattering.

$$\mu = k\lambda^3 Z^4 + 0.2 \qquad (1)$$

Equation 1

From equation 1, it is clear that a high atomic number is associated with effective x-ray absorption. As a consequence, iodine, bismuth, barium, and tantalum are the elements most frequently used to obtain high radiopacity.

Practically, radiopacity measurements of materials are made with reference to an aluminum standard. The use of aluminium, of at least 99.5% purity, is specified in the ISO standard for resin-based filling materials (ISO 4049, 1988). 9 For that, a 2 mm aluminium pellet is the required standard for the radiopacity of plastics for medical purpose (ANSI/ASTM F640-79, method C). 10

Radiopaque Polymer Blends

These systems are the most frequently described in the literature (Table 1). They are characterized by a physical mixture forming a heterogeneous dispersion with an uneven distribution of the radiopacifying agent, which is produced by suspending a radiopacifying heavy element, e.g., a metal, an inorganic salt, or an organic compound containing heavy substituents, into the polymer. 8 The most commonly used heavy elements are iodine, 11 barium, 11-27 bismuth, 18,26,28-32 zircon, 31,33 and tantalum. 38,42,43 The heterogeneity of the dispersion allows for visible separation, such as sedimentation, occurring the faster the mixture is fluid. Aggregates may form and can obstruct the percutaneously introduced implantation pathway such as the small lumen of a catheter or a needle. Concerning the deployed implant, it is worth noting that the addition of water-soluble radiopaque derivatives into the polymer structure can reduce its mechanical properties 6,34 by increased water absorption, 35 by cluster formation, or by leakage of the radiopacifying agent. Such phenomena may lead to increased fragility by enhancing default formation or propagation or both. 36

TABLE 1. Radiopaque Mixtures Used In Vivo

Polymer	Radiopaque agent	Species	Use	Year	References
IBCA	Iodine	Human	AVM	1980s	(39,41,49,130)
	Iodine	Human	GIT	1970s	(51,131)
	Iodine/Tantalum	Human	Urinary tract	1970s	(43)
	Tantalum	Human	AVM	1970s	(42,48)
	Tantalum	Dog	Aneurysm	1985	(40)
	Tantalum	Dog	GIT	1975	(38)
	Tantalum	Dog	Kidney	1976	(46)
NBCA	Tantalum	Pig	AVM	1989	(50)
	Tantalum	Rabbit/dog/human	Kidney	1978	(132)
	Iodine	Dog	Kidney	1980s	(58,65)
	Iodine/Tungsten	Human	Tumor/AVM	1990s	(60–64,66)
	Iodine	Human	Aneurysm	1994	(59)
PMMA	Barium	Human	Dental resin	1970s	(12–14,16,17,19,21,24,35)
	Bismuth	Human	Dental resin	1990	(31)
	Barium	—	Bone cement	1990s	(69,70)
PVAL	Barium	Human/dog	Kidney	1980s	(56,88)
PVAC	Iodine	Dog/human	Kidney	1984	(90)
EVAL	Iodine	Human	AVM	1990	(95)
Silicone	Tantalum	Dog	Kidney	1971	(93)
	Barium	Human	Aortic valve	1992	(133)
CA	Bismuth	Dog/human	Aneurysm	1992	(97,98)

AVM: arteriovenous malformation; GIT: gastrointestinal tract; IBCA: isobutyl 2-cyanoacrylate; NBCA: N-butyl 2-cyanoacrylate; PMMA: poly(methyl methacrylate); PVAL: poly(vinyl alcohol); PVAC: poly(vinyl acetate); EVAL: ethylene vinyl alcohol copolymer; CA: cellulose acetate.

Table 1. Radiopaque Mixtures Used In VivoAVM: arteriovenous malformation; GIT: gastrointestinal tract; IBCA: isobutyl 2-cyanoacrylate; NBCA: N-butyl 2-cyanoacrylate; PMMA: poly(methyl methacrylate); PVAL: poly(vinyl alcohol); PVAC: poly(vinyl acetate); EVAL: ethylene vinyl alcohol copolymer; CA: cellulose acetate.

Permanent radiopacity cannot be ensured by these products because chemical incorporation into the polymer is not achieved, and with time the radiopaque additives progressively leach out.

Cyanoacrylic Derivatives: Isobutyl 2-Cyanoacrylate (IBCA) and N-Butyl 2-Cyanoacrylate (NBCA)

After it was introduced by Zanetti 37 and Dotter, 38 IBCA (bucrylate) rapidly found acceptance for embolic vascular occlusion, such as for the treatment of arteriovenous malformations (AVMs). Among the many advantages offered by this derivative were low viscosity and rapid polymerization time when in contact with vascular endothelium or ionic solutions such as blood. 39-43 Superselective precise implant deposition became possible using microcatheters. 44-47 The injected fluid rapidly polymerized forming a hard intravascular cast trapping blood elements. 48

Besides an uncompleted biocompatibility evaluation for intravascular use, IBCA also exhibited some undesirable characteristics such as an exothermic reaction during polymerization, difficult to control polymerization time, lack of visibility, and possible premature polymerization inside the catheter, rendering control of implantation difficult or hazardous. To avoid premature polymerization, the use of 5% glucose solution to flush all ionic materials from the system is mandatory. 40,49 Visibility and the ability to control polymerization time were both influenced by using several additives. To avoid modifying polymerization time, micropulverized tantalum powder might be added to the mixture as suggested for the obliteration of high flow shunts. 38,42,48,49

Radiopacity with concomitant influence on polymerization time was observed by Cromwell et al., 39 as well as other authors, 41,43,49-51 describing the addition of iodinated contrast medium within IBCA. They showed that this incorporation had a nonlinear effect and modified the polymerization time over a range of 1-30 s, whereas single IBCA polymerized in less than 1 s when in contact with blood, and in approximately 3.2 s when a 50% mixture of IBCA and iophendylate oil (Pantopaque(TM)) was employed. The main disadvantage of Pantopaque(TM) is its high viscosity of more than 20 mPa.s which makes injection difficult. 52 The penetration conditions into a capillary bed of a tumor mass, or in the vessels of an AVM nidus, are also influenced by the increased viscosity, 41 and distal migration before polymerization has occurred within the vascular bed. 43

Other ways to modify polymerization time 53 used a technique based on the fact that initiation of polymerization depended on an alkaline medium, and could be inhibited by the addition of small amounts of acid. A mixture of IBCA (0.5 ml) and iophendylate oil (0.15 ml) in the presence of acetic acid (25-50 [mu]l) was tested, and showed a linear prolonged polymerization time from 1 to about 10 s. Polymerization time was shown to be prolonged by lowering the temperature of the mixture; 49 however, temperature control is difficult to apply for clinical use.

Histologic examination after embolization with IBCA showed an initial acute epithelial or endothelial inflammatory reaction, which was probably due to the exothermic reaction and to the presence of residual monomers. 54 This initial reaction was followed by an inflammatory reaction, which resolved with time, 39,40,43,51,55 similar to that seen with nonabsorbable silk sutures. In over 25 years of clinical intravascular cyanoacrylic use, no cases of carcinogenesis in humans have been observed. 56,57 However, based on the observation of a low potential to have a mutagenic effect as found in rats or using the standard Ames test, 50,57 IBCA is no longer produced.

At this time, as a substitute for IBCA, a chemically similar monomer (NBCA) was proposed as a fast polymerizing agent for the endovascular treatment of AVM. This derivative showed a shorter polymerization time than IBCA, both pure and with all subsequent dilutions by iophendylate oil or acetic acid. 50 Addition of iophendylate oil generated only a minimal linear prolongation of the polymerization time, whereas graded addition of acetic acid (0-50 [mu]l) showed a prolongation from 0.7 to about 7 s. However, a given aliquot of acetic acid produced a smaller effect in NBCA than in IBCA.

In current practice, a nonionic contrast agent (Lipiodol(TM)) is added to decrease the polymerization time of NBCA and to obtain radiopacity at the same time, 58-65 which, in our observations, is possible if the percentage of contrast agent additive is equal or higher than 50. In vitro studies showed that the polymerization time was delayed by increasing the proportion of contrast medium, and that this time was about 7 s for a mixture of a 1:3 polymer/contrast medium ratio, which provided an optimal embolization material with good flow properties.

Histopathologic reactions in tissue embolized with NBCA were either less or no more severe than those seen with IBCA, and inflammatory reactions induced by IBCA and NBCA were indistinguishable. 50 However, it is worth noting that inflammation was seen in 96% of cases with an acute reaction followed by a chronic reaction in 88%. 66

If repermeation of embolized vessels was observed in some studies, it did not seem to occur until 3 months after embolization, 59,66 and may have been due to recanalization of the clot 52 containing casts, or the development of collateral circulation that is difficult to distinguish from recanalization by radiological methods, or caused by the loss of visibility of the cast due to leakage of the radiopaque additives.

Procedural difficulties include the inability to position the implant precisely into a target and also complications have been observed with inadvertent implant placement proximal or distal to the target location. Deposition as distal as the pulmonary circulation may occur and pulmonary complications have been described by Pelz et al. 61 after embolization of brain AVMs. Use of diluting additives to render cyanoacrylates visible may thus interfere with the polymerization time and require experience to allow safe implant positioning.

Another acrylic derivative, the ethyl [alpha]-cyanoacrylate, 67 was patented as an embolic material, but no major advantages were found, and tests were conducted at a preclinical level only.

Methacrylic Derivatives: Poly(Methyl Methacrylate) (PMMA) and Poly(2-Hydroxyethyl Methacrylate) (PHEMA)

Poly(methyl methacrylate) (PMMA) has found some important applications in dental surgery 12-14,24,31,35,68 as bone cement for partial or total joint replacement 69,70 and as a percutaneous biomaterial for vertebroplasty. 71 It has also been used, similarly to PHEMA, as an embolic material by several authors, 72-75 who developed microspheres that swell in water.

Poly(methyl methacrylate) was widely employed as a dental resin, including removable dentures, temporary crown and bridge, restorative, and impression materials. Since accidental ingestion of restorative dental resins can be a serious problem (incidentally this represents approximately 8.2% of all objects removed endoscopically) 76 radiopaque dental materials 24,77-81 have been developed. The addition of inorganic fillers to PMMA does not appreciably modify hardness, solubility, and water sorption of the material, 82 but it increases compressive strength and reduces transverse strength 14,68 up to 25-34% in dry conditions and 12-21% after immersion in water for 6 weeks at 37[degrees]C (Table 2). It also decreases PMMA optical translucency and might cause a concentration of stresses leading to fracture. 13

TABLE 2. Physical Properties of PMMA Samples Containing Different Inorganic Fillers[68]

Filler (28 wt.–%)	Compressive strength (MPa)		Transverse strength (MPa)		Water absorption (%)		
	Dry	Wet	Dry	Wet	1 week	4 weeks	25 weeks
None	138	117	122	95	1.88	2.01	2.18
ZrO_2	145	128	88	79	1.39	1.44	1.56
ZnO	145	122	91	84	1.28	1.37	1.47
$BaSO_4$	142	120	90	75	1.78	1.86	2.00
$Ca_3(PO_4)_2$	154	129	80	75	1.45	1.62	1.95
MgO	147	124	90	82	2.00	3.75	11.80

PMMA: Poly(methyl methacrylate).

Table 2. Physical Properties of PMMA Samples Containing Different Inorganic Fillers 68PMMA: Poly(methyl methacrylate).

Chandler et al. 12-14 developed a formulation based on the addition of silane-treated radiopaque glass to PMMA, but this product was fragile and could cause tooth breakage. Some trials were made by adding some organo-iodine compounds to solve the problems encountered with inorganic salt incorporation. 11 The radiopacity obtained with these derivatives was satisfactory, but there were two marked disadvantages: they functioned as plasticizers and they reduced photostability.

Histological evaluation of soft tissue after implantation into the bone marrow channel and the space between the cortex and muscle of rats revealed that a thin fibrous capsule, without any sign of inflammatory cell infiltration, surrounded each radiopaque PMMA sample. 68 Since its introduction in the 60's and having proved its efficacy, PMMA has been widely used in orthopedic surgery because it allowed prostheses fixation inside the bone cavity. Radiopacity was frequently obtained by the addition of barium salts, even if that reduced mechanical strength and fracture toughness of bone cement. 69 Although the toxicity described for this derivative was quite low, in situ polymerization could cause some problems associated with the residual monomer and the exothermic reaction. However, it is important to note that radiopaque agents, which did not appear to produce an initial serious toxic effect, show some subsequent toxicity because of their slow release in soft tissue. The widely used barium sulfate has caused concern even though it has a low water solubility of only 2.5 [mu]g/ml. Another application for PMMA is for vertebroplasty procedures. Vertebroplasty consists of a percutaneous injection of PMMA cement into a lesion of a vertebral body under radiological control (fluoroscopy, CT). 71,83 The principal indication for vertebroplasty is pain due to osteolytic metastasis and myeloma, aggressive hemangioma, and osteoporotic vertebral collapse. Powder PMMA and liquid MMA are mixed prior to injection and radiopacity is ensured with tantalum or tungsten salts. The side effects observed are rare and similar to those described for other applications, including inflammatory reaction heat related damage, mass effect, and embolic potential associated with leakage of monomer into perivertebral spaces and draining veins.

Since nonbiodegradable hydrogel microspheres have found an application as an embolic material, 84,85 Thanoo et al. 74 prepared radiopaque PMMA microspheres by impregnation with barium sulfate. These radiopaque microspheres were found to be very stable over several weeks in the aqueous medium without significant leaching of barium sulfate, confirming the ability of the crosslinked polymeric network to maintain the radiopaque agent inside the microspheres. Additionally, studies on human larynx epidermoid carcinoma cell lines revealed that this methacrylic derivative was well tolerated by the cells 86 and induced a very mild tissue irritation. 87

Vinyl derivatives: Poly(vinyl alcohol) (PVAL) and poly(vinyl acetate) (PVAC)

Poly(vinyl alcohol) and poly(vinyl acetate) (PVAL) (Ivalon(R)) particles were used as an embolic material. 52,56,88 The radiopacity was triggered by the addition of inorganic salts or iodinated contrast medium. Interestingly, no resorption of the embolized area was observed. The preparation was very simple, and PVAL particles could be mixed with a relatively large amount of contrast medium (60%).

Poly(vinyl alcohol) and poly(vinyl acetate) was also used as a nonresorbable embolic material, 89,90 as a chemically stable emulsion, in which positively charged polymer microparticles were suspended in water. Microparticles are kept from aggregating in deionized water by mutual repulsion of the positive charges, whereas they aggregate immediately when released into a fluid containing anions. Poly(vinyl alcohol) and poly(vinyl acetate) also shows nonadhesive properties, that could make it a candidate for replacing cyanoacrylic derivatives, that sometimes polymerize within the catheter. Radiopacity was achieved by adding nonionic iodinated contrast medium. Poly(vinyl alcohol) and poly(vinyl acetate) emulsion has a low viscosity ranging from 2.0 to 3.1 mPa.s., depending on the concentration of PVAC and the proportion of contrast medium. When concentrated emulsion is injected, it will stay in the arteries and migration of free particles is unlikely to occur. The concentration of the emulsion should be at least 7% for arterial occlusion, and 10% or more for the treatment of AVMs. Poly(vinyl alcohol) and poly(vinyl acetate) emulsion can be considered as nontoxic because neither macroscopic inflammation nor necrosis has been described, and it triggers only mild cellular infiltration, confined to the immediate surroundings. Even when PVAC is hydrolyzed, it produces only a tiny amount of acetic acid.

Hyaluronate gel

Some authors have used the Hylan(TM) gel to embolize AVMs, vascular tumors and to treat hemorrhages. 91 This embolization gel is composed of crosslinked sodium hyaluronate, microcrystalline cellulose, hexamethonium chloride, and thrombin. Hylan(TM) gel is viscoelastic, pseudoplastic, thrombogenic (thrombin component), and made radiopaque by addition of a tantalum component. Hylan gel/blood clots formed were solid, intact bodies without exclusion or loss of gel or blood components, and tantalum remained part of the clot, and is not released from the gel. Hylan(TM) gel is nontoxic, noninflammatory, and nonimmunogenic.

Silicone

Due to its excellent biocompatibility and nonbiodegradability, silicone has also been used as an embolic material, 56,92,93 even if it is worth noting that recent studies reveal the possible mutagenicity of silicone polymer. Silicone fluid mixture containing a catalyst necessary for polymerization has been used clinically. 52 Complete flow stasis was used to facilitate the injection and polymerization of the silicone fluid in the target region. Radiopacity was ensured with tantalum powder. No inflammatory response was described, even if minimal foreign body giant cell reaction was seen. The main disadvantage of silicone fluid embolization is related primarily to the difficulty in mastering injection to avoid the risk of pulmonary embolization. Another way to use silicone resin as an implant is in the form of silicone beads. For this purpose, silicone resin is cured in an aqueous medium using poly(vinyl alcohol) as suspension stabilizer to generate microspheres. 56,92,93 Incorporation of a radiopaque agent such as barium sulfate or methyl iothalamate was found to destabilize the suspension. In contrast, radiopaque tantalum powder could be encapsulated without affecting the stability, although it led to the formation of larger microspheres.

Polyurethanes

Because the various kinds of polyurethanes have found a large number of biomedical applications owing to their interesting properties, and satisfactory biocompatibility, Thanoo et al. 94 developed tantalum-loaded polyurethane microspheres. They proved that the addition of a radiopacifying agent did not modify the size distribution of the microspheres, which was determined by the stabilizer concentration. Toxicity studies were limited to demonstrating the nonhemolytic behavior of these radiopaque microspheres in in vitro tests.

Ethylene vinyl alcohol copolymer (EVAL)

Another nonadhesive embolic biomaterial was developed by Taki et al. 95,96 This copolymer EVAL consisted of 0.67 mol of ethylene and 0.33 mol of vinyl alcohol, and thus showed both hydrophobic and hydrophilic properties. Metrizamide powder was added as a contrast medium to enhance the radiopacity of this derivative. Injection was possible after dissolution in dimethyl sulfoxide (DMSO). Ethylene vinyl alcohol copolymer was considered as biocompatible, and associated with minimal inflammatory reaction, no biodegradability, and showed comparable embolic properties to IBCA.

Cellulose acetate

Mandai et al. 97 and Kinugasa et al. 98-104 developed a cellulose acetate liquid material for the embolization of aneurysms. They solubilized the polymer in DMSO and added bismuth oxide as radiopacifying agent. The material shows a low viscosity and precipitates in a hard mass when in contact with aqueous media. Few inflammatory cells were observed, and the reaction did not extend to either the vessel wall or the surroundings.

Another technique developed in order to use cellulose acetate as an embolic material was to prepare microspheres. 105 These microspheres could be made radiopaque by the incorporation of a tantalum salt. Preliminary studies in rats showed that these microparticles were useful for the treatment of cancerous tumors.

It is worth noting that Chaloupka et al. 106 described a controversial observation on local vessel and pig brain tissue toxicity of DMSO, concluding initially that this solvent could be too toxic for intravascular application. However, the same authors claimed that, based on subsequent studies, these local toxic effects are dose-related and that DMSO could be considered as a solvent for clinical application when used in low doses. 107

Radiopaque Polymer Salt Complexes

Radiopaque polymer salt complexes were proposed to control dental filling radiologically using acrylic resins. These systems were produced by the incorporation of a radiopaque, heavy metal salt into an appropriate polymer ligand via chelation, a technique which could be applied to a broad range of polymers. 31 The resulting systems are homogeneous and show both polymeric and ionic character. The types of polymers used as ligands for chelation typically contain a polar section that can strongly bind cations, and, frequently, a nonpolar part that allows solubilization in nonpolar media. This property enables them to dissolve inorganic salts in low polarity organic media.

The polymeric ligands can chelate a wide range of inorganic salts, such as barium, cesium, bismuth, lead, or mercury derivatives, in order to produce single-phase systems. Limiting release and constant radiopacity are ensured by entrapment of the polymer-salt complex in a crosslinked, interpenetrating network. 8 This complex, however, is a noncovalent binding and it is worth noting that the halogen functional groups might tend to hydrolyze or degrade and, consequently, form leachable compounds. Release of radiopaque salts is favored by the presence of acidic aqueous fluids, commonly present in living tissue. In addition to the potential toxic effects, the leaching of bromide and other halogens leads to discoloration of the resin, which gradually converts the polymer to a radiolucent material. Moreover, presence of halogenated organic additives may also contribute to the degradation of the polymer. Table 3 summarizes some experiments in the radiopaque polymer salt complexes field.

TABLE 3. Radiopaque Complexes

Polymer	Radiopaque agent	Use	Year	References
Copolymers MMA-MG22	Barium	In vitro	1985	(108)
Copolymer MMA-HEMA	Iodine	Embolization	1997	(134)
PMMA	Bismuth	Dental resin	1980s	(10,30,31,111)

PMMA: Poly(methyl methacrylate); MMA: methyl methacrylate; HEMA: hydroxyethyl methacrylate.

Table 3. Radiopaque ComplexesPMMA: Poly(methyl methacrylate); MMA: methyl methacrylate; HEMA: hydroxyethyl methacrylate.

Methyl Methacrylate Derivatives

Methyl methacrylate derivatives (MMD) copolymers and a commercially available methacrylate, with an average of 22 ethylene oxide units (MG22), were synthesized and chelated with barium bromide. 108 However, permanent radiopacity was not achieved with these derivatives, and this limited their potential for clinical application.

Another approach was developed by Smid et al. 10 who used cation-chelating monomers to achieve complete solubilization of heavy metal salts. The authors tried to form heavy-metal compounds which were chelated or solubilized to obtain a single phase with the macromolecular structure of the resin, which was optically transparent and inherently resistant to degradation. They developed blends of PMMA and heavy metal salts by dissolving bismuth tribromide ($BiBr_3$) or, sometimes, bismuth chloride 10,30,31,109 in MMA up to about 40% by weight. The high solubility of the salt resulted from the interaction between the carbonyl group and bismuth, because the electron donating monomer would readily interact with radiopacifying heavy metal Lewis acid salts such as bismuth tribromide. This was demonstrated by infrared spectroscopy, ^{1}H- and ^{13}C-NMR spectroscopy of carbonyl-containing compounds, in which bismuth salts were dissolved. 10,30,110 Obviously, clear solutions of $BiBr_3$ could also be obtained with other monomers containing a carbonyl functional group. Finally, the MMA/$BiBr_3$ mixture was also polymerized to form solid transparent resins.

The presence of about 40 wt-% of the salt decreased the molecular weight of the PMMA from 120,000 to about 80,000 $g.mol^{-1}$, 10,30 and slightly increased the glass transition temperature from 108[degrees]C to 123[degrees]C. 109 Moreover, the aqueous stability of the PMMA-$BiBr_3$ resins, which developed opaqueness on contact with water and the deactivation of the polymerization initiator caused by its complex formation with the bismuth salts, need to be improved. The influence of the $BiBr_3$ content in PMMA on biocompatibility was tested by the Ames assay revealing no sign of mutagenicity. However, a small but significant increase in the time-distance cytotoxicity index (TDCI) in gingival epithelial cell culture was observed, which was correlated to the amount of $BiBr_3$ additive 31 (Table 4).

TABLE 4. Biocompatibility of $BiBr_3$-Containing PMMA Resins as Determined by Cytotoxicity in Gingival Epithelial Cell Culture[31]

Material (% $BiBr_3$ in PMMA)	Viability index (cells/mm^2)	Cytotoxicity TDCI*
0	370	0.3
5	342	7.8
10	333	10.2
15	346	6.7
20	328	11.6

* A time-distance cytotoxicity index (TDCI) was determined by measuring the average number of surviving cells at two radial distances from three specimens after two exposure times, normalized to a control.
PMMA: poly(methyl methacrylate).

Table 4. Biocompatibility of $BiBr_3$-Containing PMMA Resins as Determined by Cytotoxicity in Gingival Epithelial Cell Culture 31* A time-distance cytotoxicity index (TDCI) was determined by measuring the average number of surviving cells at two radial distances from three specimens after two exposure times, normalized to a control.PMMA: poly(methyl methacrylate).

Radiopacities of 1 and 2 mm thickness PMMA pellets, expressed in millimeters of aluminium, were plotted as a function of the weight-% of $BiBr_3$, varying from 2.3 to 33 wt-%. The results showed a linear relationship for 1 mm pellets, and that a 2 mm PMMA pellet containing about 14 wt-% $BiBr_3$ had a radiopacity equal to that of 2 mm of aluminium, which is the specified standard for the radiopacity of plastics for medical use. 10,30 Figure 2 shows variations of radiopacity with polymer thickness.

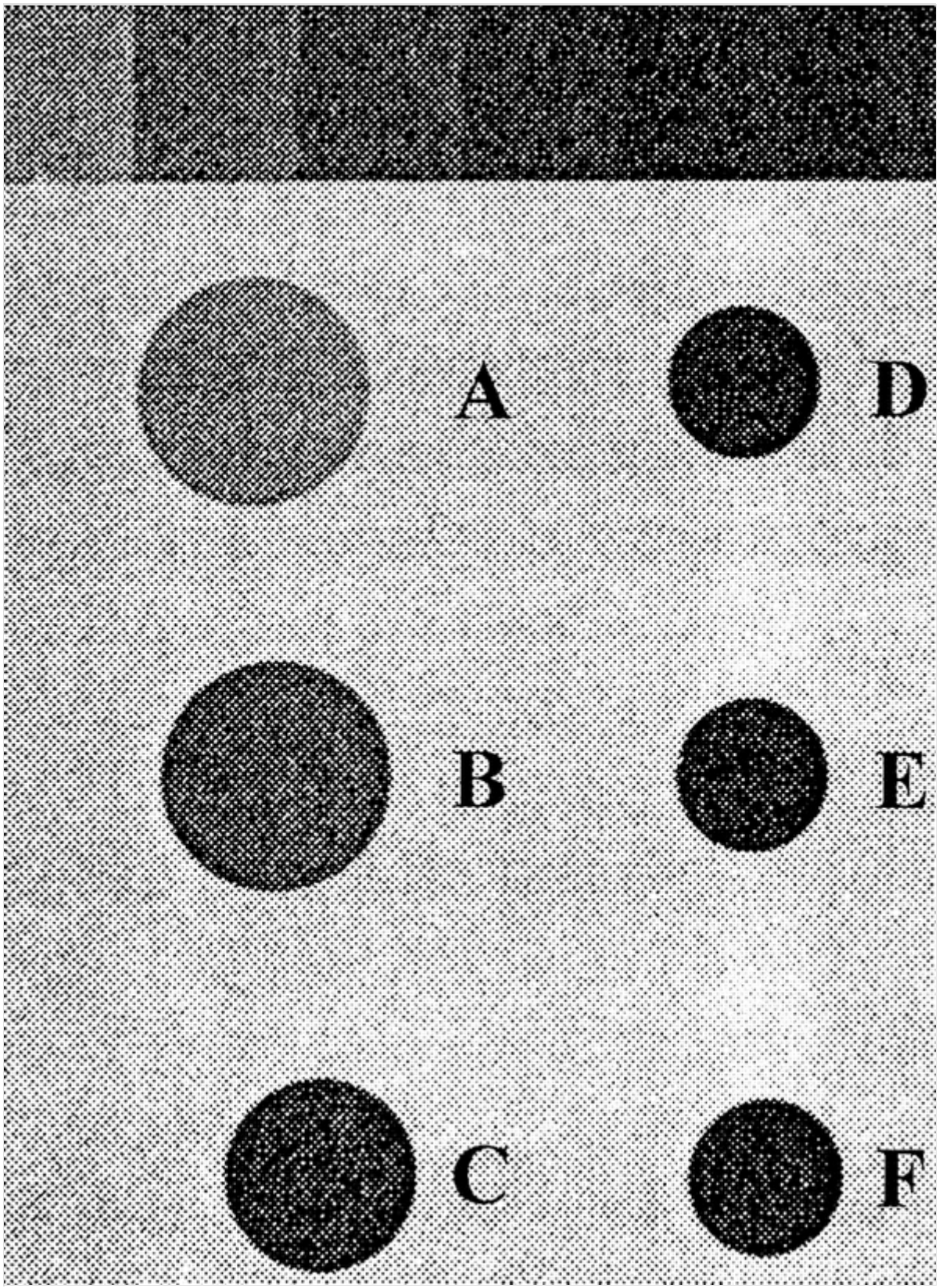

Figure 2. Variations of radiopacity with thickness of material. Positive radiograph of a homogeneous PMMA 20 wt-% $BiBr_3$ (2% resin cross-linked); thickness: (A) 1.0 mm; (B) 1.85 mm; (C) 2.9 mm; (D) 4.0 mm; (E) 5.0 mm; (F) 5.7 mm. (modified from Silberman-Hazony et al.) 8

In the same way, Rawls 28 and Delavitz 110-114 developed a PMMA containing an organobismuth radiopacifying additive. The x-ray contrast agent used, triphenyl bismuth, was soluble up to 70 wt-% in MMA, and did not affect the polymerization process. A minimum of 23 wt-% of halogenated derivative was necessary to obtain the same radiopacity as the aluminum standard.

As a side effect, this bismuth compound acted as a plasticizer and the glass transition temperature was lowered by 1.3[degrees]C/wt-% Ph_3Bi. 115 With regard to stability, it is noticeable that the insensitivity of Ph_3Bi to moisture keeps composites clear, and that its water insolubility avoids leaching out in an aqueous environment. In addition, these composites are stable to heat and are also stable in air. Finally, Ph_3Bi does not easily form adducts with the polymerization initiator, unlike the bismuth halides and, therefore, does not compete with the polymerization.

Although a slight elevation in cytotoxicity was described, which was most likely due to a reduction in monomer conversion resulting from the additional heat capacity of Ph_3Bi, 29 Ph_3Bi shows a lower toxicity, both alone and when in combination with PMMA, with a magnitude that is similar to the toxicity of PMMA alone.

Other radiopaque derivatives could be obtained in the same way using triphenyl bismuth and polystyrene, poly(vinyl chloride), or polyethylene, but have found limited medical applications compared to polymethacrylate derivatives.

Radiopaque Polymerized Monomers

Because of the problems encountered with the radiopaque salt mixtures and complexes, there is an interest in radiopaque materials, where a radiopacifying derivative is molecularly bound to the polymer. Such polymers could form clear, homogeneous, nonleachable materials with mechanical properties, which are substantially equivalent to those of the parent polymers.

These systems are produced by introduction of the radiopacifying element electrovalently or covalently into the polymer backbone (Table 5). Unfortunately, the major disadvantage of radiopaque polymer systems in which the radiopacifying agent is electrovalently bound is the susceptibility to hydrolysis, which may prevent permanent radiopacity with time. The main drawback of covalently bound radiopaque systems is their relatively high production cost. 8

TABLE 5. Radiopaque Monomers

Polymer	Radiopaque agent	Use	Year	References
Acrylic acid	Barium	Dental resin	1971	(116)
MMA	Bismuth	In vitro	1990s	(110,111,115)
	Bromine	Dental resin	1982	(6,118)
	Iodine	In vitro	1995	(119)
MMA/HEMA	Iodine	Stent	1990s	(36,120,123–126)
PHEMA	Iodine	Embolization	1990s	(72,75,121,122)
PE	Iodine	Contrast agent	1991	(127)
PU	Bromine	Catheter	1993	(128)
Starch	Iodine	Contrast agent	1981	(129)

MMA: methyl methacrylate; HEMA: Hydroxyethyl methacrylate; PHEMA: poly (2-hydroxyethyl methacrylate); PE: polyester; PU: polyurethane.

Table 5. Radiopaque MonomersMMA: methyl methacrylate; HEMA: Hydroxyethyl methacrylate; PHEMA: poly (2-hydroxyethyl methacrylate); PE: polyester; PU: polyurethane.

Acrylic acid derivatives

During the 70's, Combe et al. 27,116 proposed the incorporation of heavy metal elements into dental acrylic materials. They prepared barium acrylate by adding acrylic acid to a suspension of barium hydroxide in water. The water-soluble barium-acrylate formed was polymerized by heating at 50[degrees]C, in the presence of ammonium persulfate as initiator. The insoluble poly(barium acrylate) obtained was isolated, and showed extensive crosslinking due to the presence of divalent barium ions. Barium acrylate was also copolymerized with methyl methacrylate by refluxing the two monomers in an acetone-water mixed solvent system. Nevertheless, addition of barium weakened and reduced the impact and transverse strengths of the resins, even though it had very little effect on the hardness. Combe explained these results by the crosslinked structure of poly(barium acrylate), because crosslinking generally forms harder and more brittle polymers, and affects their solubility. Thus, barium induces a higher brittleness in the acrylic resins and increases the quantity of monomer required to form a satisfactory dental dough. Moreover, the ionic nature of the barium acrylate could lead to the absorption of significant amounts of water, while slow hydrolysis of the resins leads to the loss of the opacifying atom. 6

Methyl methacrylate derivatives

The interesting properties of triphenyl bismuth led Smid et al. 112 and other investigators 114,115,117 to study monomers containing a phenyl bismuth moiety, and they proposed binding the radiopaque element to the resin backbone using bismuth monomers. Transparent, hard materials were obtained by copolymerizing MMA and styryldiphenylbismuth at 65[degrees]C with benzoyl peroxide as initiator. The synthesized products had a glass transition temperature of 100-110[degrees]C, close to that of PMMA because the heavy metal was part of the backbone of the products. Thus, the thermal and mechanical properties of the polymers, in comparison to materials containing heavy metal components as additives only, were improved. Permanent, chemical incorporation into the polymer structure prevented the leaching out of the heavy metal x-ray contrast agent in any kind of solvent. Identical copolymerization could be obtained with other monomers such as styrene or other vinyl monomers. 110

Another approach to opacify PMMA has been patented by Causton, 118 and lately improved by Davy et al., 6 who attempted to incorporate bromine into the PMMA resin. They synthesized 2,3-dibromopropyl methacrylate by refluxing methacrylic acid and 2,3-dibromopropanol in toluene. The product obtained was a colorless liquid with a boiling point of 82-86[degrees]C. It is possible to polymerize the 2,3-dibromopropyl methacrylate to obtain a homopolymer that possesses high bromine content (55.9 wt-%) and, hence, highly satisfactory radiopacity, but unfortunately it is also highly brittle. In order to improve the mechanical properties of the brominated polymer, copolymerization of poly(2,3-dibromopropyl methacrylate) with methyl methacrylate at 70[degrees]C using azo-isobutrylnitrile as initiator was required.

The synthesized copolymers had a crosslinked structure, and their water absorption at equilibrium decreased with increasing poly(2,3-dibromopropyl methacrylate), reflecting the hydrophobic nature of the resin. Upon increasing the fraction of poly(2,3-dibromopropyl methacrylate), the effect upon the impact strength and tensile strength was minimal until 60% of the brominated polymer was reached, where upon significant loss of strength was observed above this level. The flexural strength decreased continuously while the elasticity modulus increased proportionally to the content of the brominated polymer.

Finally, synthesis and polymerization of iodine-containing methacrylates have been investigated. Moszner et al. 119 highlighted that variable radical polymerization behavior was exhibited when comparing similar methacrylic monomers. For example, 2,4,6-triiodophenyl methacrylate showed a poor tendency to homopolymerization and gave only oligomeric products, whereas 2,3,5-triiodobenzoyloxyalkyl methacrylate yielded polymers with number-average molecular weights of about 58,000-147,000 under similar conditions (Figure 3).

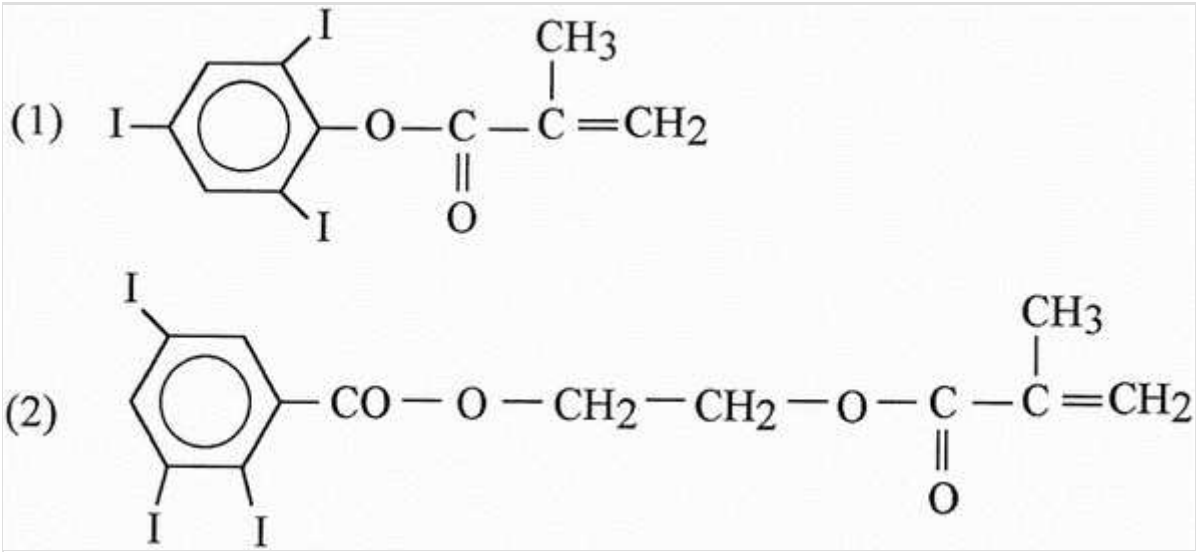

Figure 3. Structures of 2, 4, 6-triiodophenyl methacrylate 1 and 2, 3, 5-triiodobenzoyloxyalkyl methacrylate 2 (from Mozner et al.) 119

The different polymerization behavior of the iodine-containing monomers was also shown in their copolymerization with MMA. Whereas, 2,4,6-triiodophenyl methacrylate reduced the MMA polymerization and thus decreased the number-average molecular weight of the formed polymers, 2-methacryloyloxyethyl 2,3,5-triiodobenzoate favored the MMA polymerization by increasing monomer conversion.

Hydroxyethyl methacrylate derivatives

Highly porous microspheres for endovascular occlusion were prepared by suspension polymerization of low crosslinked PHEMA in the presence of polymeric diluents such as PMMA, or crosslinking agents such as ethylene glycol dimethacrylate, or ethylene dimethacrylate. These spherical hydrogel particles were made radiopaque by esterification of their reactive hydroxyl groups with triiodobenzoic acid derivatives or nontoxic contrast media used clinically, such as iothalamic or iopanoic acid. 72,120-122 Nevertheless, homo- and copolymerization of iothalamic ester of HEMA with HEMA and MMA failed to give high molecular weight polymers, 123 probably because of the presence of bulky iodine atoms in the monomers which sterically hinder the polymerization propagation step. 120 In contrast, Horak et al. 72 found that copolymerization of the triiodobenzoic acid derivative with HEMA was possible.

Sufficient radiopacity was obtained by binding 25 to 30 wt-% iodine, even though it was possible to bind more than 40 wt-% iodine to the resin backbone. However, such microspheres with high iodine content were found to be hard, brittle, less hydrophilic, and nonswelling.

The incorporation of iodine into the resin backbone did not decrease the water absorbing capacity of the microspheres. Indeed, nonradiopaque microspheres possessed an equilibrium water content (EWC) of about 62%, while microspheres containing 29 wt-% iodine had an EWC still superior to 40%, 122 even though many of the reactive hydroxyl functions had been used in the acetylation reaction. This high water absorbing capacity was attributed by Jayakrishnan et al. 122 to the highly porous structure of the microspheres.

Preliminary subcutaneous implantation studies of the iodinated microspheres in rats or rabbits did not demonstrate adverse tissue reactions. 75,122 Histological examination indicated that radiopaque emboli did not cause any damage or inflammation to the surrounding tissue. Encapsulation of the emboli was observed, accompanied by the formation of a thin fibrous capsule. Fibroblast and occasional endothelial cell infiltration into the pores of the material indicated its partial organization, which was more pronounced in the peripherally bead. At the bead surface, only sporadic giant cells of foreign bodies could be detected, which were regarded as evidence of the weak character of the resorption reactions. This confirmed the biological compatibility of the embolic material, which underwent virtually no resorption in the living organism. It might be assumed that the porosity of the material, which enabled it to be penetrated by the connective tissue cells, was the factor favoring fixation of the emboli in the blood vessel lumen. Moreover, these iodinated particles did not cause any blood hemolysis, 120 whereas they promoted blood coagulation and would be particularly suitable for patients with pronounced blood hypocoagulation. 75

Radiopaque HEMA could also be used as a terpolymer composed of iodo-methacrylate derivative, MMA, and HEMA in the molar ratio 21:60:19. 123-126 Radiopaque iodo-methacrylate was obtained in a standard esterification reaction between HEMA and 4-iodobenzoic acid, and utilized in the terpolymer synthesis via a radical polymerization reaction at elevated temperature. It has been found that at least approximately 20 mol-% ought be used to ensure an excellent x-ray visibility, even in thin fibers, which suggests that it is a promising material for endovascular stent.

Characterization of the terpolymer showed a glass transition temperature of about 79[degrees]C, and a weight-average molecular mass of about 43,100 $g.mol^{-1}$. ^{1}H-NMR and ^{13}C-NMR spectroscopy established the structure of the derivative, and confirmed that approximately 21 mol-% iodine-containing building block was chemically bound to the material. The spectra also showed the presence of traces of residual monomers (less than 1%). The dynamic contact angle was also measured to evaluate the hydrophilicity/hydrophobicity of the material, and showed a lower value than PMMA due to the presence of hydrophilic HEMA.

Hemocompatibility was also studied to ensure that this derivative was appropriate as an endovascular stent. It was compared with polyethylene (PE) and poly(vinyl chloride) (PVC), which are regarded as relatively thrombogenic and inert materials, respectively. The results showed that the radiopaque terpolymer exhibited low in vitro thrombogenicity, comparable to PVC, probably due to the presence of HEMA. Microscopic evaluation after subcutaneous implantation in rats showed that this derivative was well tolerated by the subcutaneous tissues. 36 Therefore, it could be claimed that this material was not toxic, biologically inactive, and not degraded by the host. No signs of necrosis, abscess, tissular reactivity, cellular immobilization, or inflammation have been observed.

Finally, it seemed that this terpolymer had interesting applications as an endovascular stent because it is markedly less thrombogenic than metals, currently used for the construction of stents, and it is possible to locate the stent during the implantation process. Its nonbiodegradable behavior, however, may be considered a drawback.

Polyesters

In 1991, Jay et al. 127 patented the development of a tetraiodophenolphtalein polyester as a new reticuloendothelial specific intravenous contrast agent for the enhancement of liver and spleen in computerized tomography scanning (CT). They prepared biodegradable nanoparticles of this derivative by reacting a solution of sodium tetraiodophenolphtalein in borate buffer containing dextran with succinyl chloride dissolved in dichloroethane. The resulting suspension was centrifuged, the sedimented nanoparticles isolated and suspended in glucose 5% prior to administration. Iodine content inside the tetraiodophenolphtalein polyester was 58 wt-%, and CT images of intravenous injection in rabbits demonstrated marked and selective enhancement of liver and spleen, which gradually declined over a period of 2-3 weeks.

Determination of other effects was evaluated from serial blood samples obtained during the 2 weeks following the administration of the contrast agent. Tests showed no abnormalities in liver enzymes, or in bilirubine, creatinine, or electrolytes.

Polyurethanes

Because the first radiopaque polyurethanes catheters or cannulas developed were not sufficiently soft in isotonic fluids and showed a high flex modulus owing to their high radiopaque agent content, Sarpeshkar et al. 128 developed and patented the synthesis of transparent radiopaque polyurethanes with high halogen content, exhibiting better flexibility under physiological conditions. Therefore, previously used halogenated polyols or polyisocyanate chain extenders were replaced by hydrophilic structural units containing nonionic or ionic groups. For example, when using a chain extender such as dibromoneopentyl glycol, the desired bromine content (about 25 wt-% of polyurethane) could be achieved only by using a relatively large quantity of this product, which resulted in a comparatively large hard segment content and resulting disadvantages such as irritation or roughness. The authors showed that it was, therefore, possible to obtain optically transparent radiopaque polyurethanes that had high halogen content and that were soft by replacing partially (or completely) the previously reported brominated chain extenders with tetrabromodipentaerythritol.

Starch

Cohen et al. 129 described the preparation of iodinated starch suspension as a model particulate hepatic contrast agent. This triiodobenzoyl derivative of starch, containing about 61% iodine covalently bound, forms a suspension that is stable and is composed of particles of up to 4 [mu]m. The biodistribution study demonstrated that satisfactory contrast was obtained in the liver and spleen, because the material was taken up by the reticuloendothelial cells. Limited acute toxicity studies were performed in mice and showed that the intravenous LD50 at 7 days was approximately 0.9 g/kg body weight and that animals receiving sublethal doses showed no visible signs of distress.

Conclusion

Since the introduction of radiopaque derivatives as diagnostic agents, many polymeric materials have been investigated for biomedical use. Broad experience has been gained in the field of radiopaque polymers for dental restorations or diagnostic contrast materials. With the advent of minimally invasive percutaneous treatments performed under fluoroscopy (DSA, CT), ultrasounds, or open MRI, there is a need to further develop radiologically visible implants. Although several authors have tried to develop other radiopaque derivatives, to date very few have found an in vivo application.

The first radiopaque polymers developed were characterized by the incorporation of radiopacifying salts as physical admixtures into the resin, and these are still commonly used because of their easy preparation. A major disadvantage common to this approach is the phase separation due to the incompatibility of highly polar, ionic radiopaque substances with low polarity resins, that lead frequently to the degradation of physical and mechanical properties. Single-phase radiopaque polymers were developed by incorporating radiopacifying elements into the polymer backbone via chelation in order to reduce the major drawback of the physical admixture of salts. Radiopaque element entrapment into the crosslinked, interpenetrating network limits diffusion and satisfactory radiopacity is ensured. However, radiopacity can decrease with halogen group hydrolysis or decomposition that results in the formation of leachable derivatives. Finally, development of homogenous, radiopaque polymeric materials has been studied by the polymerization of radiopaque monomers, which possess a radiopacifying element introduced electrovalently or covalently into their unit prior to polymerization. This last approach seems to be the most appropriate leading potentially to stable radiopaque polymers with properties equivalent to the nonopaque, parent polymers. It is worth noting that research will be carried out in the near future in an interdisciplinary approach to find out new biocompatible radiopaque polymers.

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KEY WORDS. Biomaterials; radiopacity; x-ray imaging; radiopaque polymers; polymers; implants; inserts; review.

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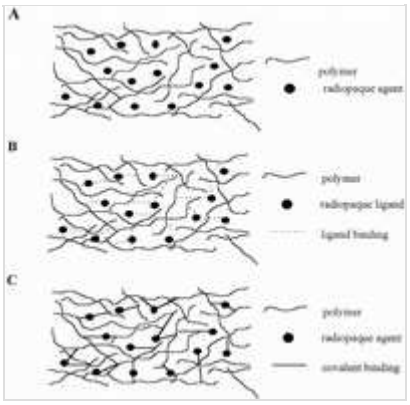
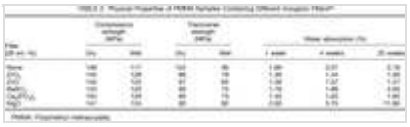


☐ Figure 1

$$\mu = k\lambda^3 Z^4 + 0.2 \qquad (1)$$

☐ Equation 1

☐ Table 1



☐ Table 2

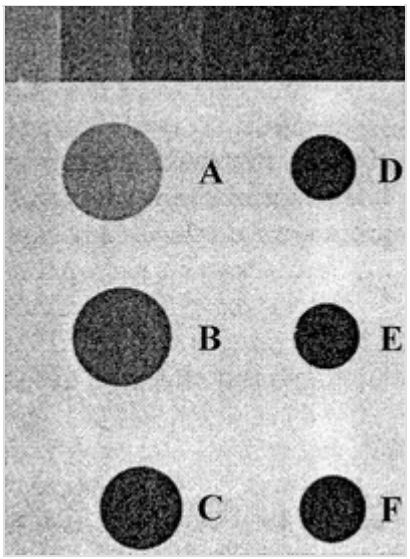
☐ Table 3

TABLE 4. Biocompatibility of $BiBr_3$-Containing PMMA Resins as Determined by Cytotoxicity in Gingival Epithelial Cell Culture[21]

Material (% $BiBr_3$ in PMMA)	Viability index (cells/mm²)	Cytotoxicity TDCI*
0	370	0.3
5	342	7.8
10	333	10.2
15	346	6.7
20	328	11.6

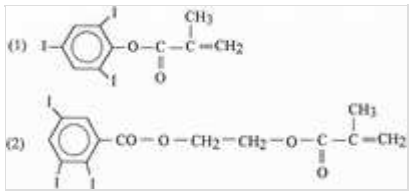
* A time-distance cytotoxicity index (TDCI) was determined by measuring the average number of surviving cells at two radial distances from three specimens after two exposure times, normalized to a control.
PMMA: poly(methyl methacrylate).

☐ Table 4



☐ Figure 2

☐ Table 5



☐ Figure 3

Retour au début