Synthesis and Polymerization of Some Iodine-Containing Monomers for Biomedical Applications

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SYNOPSIS

Triiodophenol and iothalamic acid (5-acetamido-2,4,6-triiodo-*N*-methyl isophthalamic acid) were converted to their acrylic derivatives by esterification with methacryloyl chloride and 2-hydroxyethyl methacrylate (HEMA), respectively. The monomers due to presence of heavy iodine atoms were expected to be radiopaque in nature. The monomers were characterized using TLC, IR, and ^{1}H-NMR spectroscopy. Both monomers were highly resistant to homopolymerization and copolymerization with other acrylic monomers such as methyl methacrylate (MMA) or HEMA by initiators such as 2,2'-azobis isobutyronitrile (AIBN) or benzoyl peroxide (BPO) yielding only polymers of low molecular weight. The polymers obtained were characterized by gel permeation chromatography (GPC) and differential thermal analysis (DTA). The resistance to polymerization is presumably due to the presence of bulky iodine atoms in the monomers sterically hindering the propagation step. The decomposition temperatures of the homopolymers and copolymers were close to 300°C. Copolymers of HEMA with both radiopaque monomers incorporated to the extent of 25 wt % in the feed, however, produced polymers with good radiopacity. Copolymers with HEMA were also prepared in the form of microspheres by a solvent evaporation method with the aim of using them as particles in therapeutic embolization. While the polymer based on triiodophenol was found to cause extensive blood haemolysis in in vitro tests, polymer based on iothalamic acid was found to be nonhemolytic in character suggesting that copolymers based on iothalamic acid would be suitable for implantation in the living tissue.

INTRODUCTION

Radiopacity is a desirable property of implants used in surgery as it allows postoperative assessment of the fate of the implant using X-radiography. Though most metallic implants used in surgery are highly opaque to X-rays, implants based on polymeric materials are often not radiopaque in nature. In order to impart the necessary degree of radiopacity to such implants, radiopaques such as barium sulfate or bismuth halides are sometimes incorporated in them when they are produced by molding, casting, extrusion, etc. The incompatibility of inorganics such as barium, bismuth, or silver with the polymer matrix often affects the physical and mechanical properties of the implant adversely. Moreover, the possibility of the inorganic ions leaching into the body fluid over long periods of time also poses a threat both from the standpoint of the stability of the implant and the toxicity of the metal ions.[1]

The best possible alternative to such problems would be to synthesize monomers having covalently bound halogen atoms such as iodine or bromine and polymerize those monomers. Monomers that possess radiopaque properties can either be copolymerized in small quantities with other monomers that constitute the bulk of the implant or the homopolymer of a radiopaque monomer can be blended with other polymers to prepare the implant. Not many such monomers and polymers have been reported in the literature yet. Barium and zinc acrylates[2] have been

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reported that can be copolymerized with methyl methacrylate (MMA). However, the ionic nature of these resins leads to significant absorption of water and the slow hydrolysis of poly(zinc acrylate) leads to the loss of the opacifying atom.[3] Recently, polymers and monomers that solubilize heavy-metal salts such as barium bromide, bismuth halides, uranyl nitrate, and lanthanides have been investigated by Cabasso et al.[4] These authors have also prepared polymer salt complexes of bismuth bromide and uranyl nitrate with acrylated polyphosphonates.[5] The phosphoryl group is believed to provide a strong coordinating site to the metal ion. To the best of our knowledge, the only halogen-containing comonomers mentioned in the literature to impart radiopacity to implants are bromo methacrylates such as 2-bromoethyl methacrylate, 2,3-dibromopropyl methacrylate, and tribromophenyl methacrylate, which are copolymerized with MMA in preparing dental implants.[3,6] No iodine-containing acrylates have apparently been investigated. We have recently reported that clinically used nontoxic radiocontrast substances based on iopanoic acid [3-(3-amino-2,4,6-triiodophenyl)-2-ethyl propionic acid] and iothalamic acid could be chemically bound to poly(2-hydroxyethyl methacrylate) (PHEMA) to impart radiopacity to the polymer.[7] In view of the fact that iodine is a heavier atom compared to bromine and since iodine-containing dyes are routinely used in interventional radiology, it was felt worthwhile to study the synthesis and polymerization of some iodine-containing methacrylates. Thus we synthesized triiodophenyl methacrylate and the iothalamic ester of 2-hydroxyethyl methacrylate (HEMA). This study reports on the synthesis, characterization, and polymerization of these monomers and a preliminary toxicity evaluation of their polymers.

EXPERIMENTAL

Materials

HEMA, MMA, and ethylene glycol dimethacrylate (EGDM) were purchased from Aldrich (U.S.A.) and were distilled under vacuum before use. Phenol (Glaxo, India), thionyl chloride (Romali, India), and tetrahydro furan (THF) (E. Merk, India) were dried as per standard procedures, distilled, and used. Silver nitrate (E. Merk, India), iodine monochloride (SD, India), methacrylolyl chloride, *N,N*-dimethyl amino pyridine, and triethyl amine (Aldrich, U.S.A.) were used as received. Iothalamic acid was prepared by precipitation from sodium iothalamate solution (Conray 420, May & Baker, India) by acidification, followed by washing with water and drying in an air oven. And 2,2′-azobis isobutyronitrile (AIBN) and benzoyl peroxide (BPO) were recrystallized twice and used. Solvents such as hexane, chloroform, and ether were of analytical or equivalent grade.

Methods

Esterification of Iothalamic Acid with HEMA

Iothalamic acid was converted to its acid chloride by refluxing 10 g of the powdered acid with 50 mL of thionyl chloride in presence of 0.5 mL of dimethyl formamide (DMF) for about 8 h. Excess thionyl chloride was removed by distillation, and the final product was crystallized from a concentrated solution in chloroform by portionwise addition of dry hexane under cooling in ice. The product obtained was then dried in vacuum.

Into a solution of 2.86 g (22 mmol) of HEMA and 2.44 g (20 mmol) of dimethyl amino pyridine in 100 mL THF taken in a 250-mL round-bottom flask was added slowly 12.65 g (20 mmol) of iothalamyl chloride dissolved in 100 mL of THF using a pressure-equalized addition funnel. The solution was kept stirred at 0–5°C during the addition using a magnetic stirrer. After the reaction was allowed to proceed for 40 h at room temperature (RT), the THF was removed using a rotavapor at RT. The product obtained, iothalamic ester of HEMA (IEH), was washed with dilute HCl followed by dilute $NaHCO_3$ and finally with water and dried in vacuum. Yield 90%.

Acylation of Methacryloyl Chloride with Triiodophenol

Phenol was converted to triiodophenol by treating with INO_3, which was formed by the reaction between $AgNO_3$ and ICI.[8] The product obtained was recrystallized from chloroform. Triiodophenol (4 g, 8.5 mmol) and triethyl amine (12 g, 10 mmol) were dissolved in 100 mL THF in a 250-mL round-bottom flask and 1.2 g of methacrylolyl chloride (10 mmol) dissolved in 25 mL of THF was slowly introduced into the flask using a pressure-equalized addition funnel while the solution was kept stirred at 0–5°C. The reaction was allowed to proceed at RT for 30 h. The solvent was evaporated using a rotavapor, the residue was taken in 30 mL of ether, washed with dilute HCl, dilute $NaHCO_3$, and finally with water. The ether layer was dried over anhydrous sodium sulfate over night, and the ether was evapo-

rated at low temperature in a flash evaporator to give triiodophenyl methacrylate (TIPM) in 85% yield.

Characterization of the Monomers

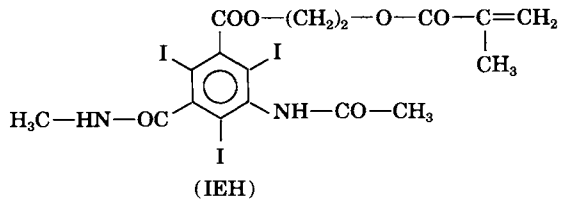
The purity of the monomers was checked by TLC (E. Merck, Type 60, F-254) using ethyl acetate as the eluent. The infrared spectra of the monomers were recorded in a Perkin-Elmer spectrophotometer (model 597), and the ^{1}H NMR spectra were recorded in a Jeol instrument (F 90Q) with DMSO-d_6 as the solvent and TMS as the internal standard.

Polymerization and Polymer Characterization

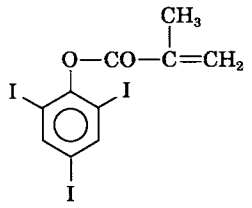
A 10% solution of the monomers (IEH or TIPM) in methanol was homopolymerized and copolymerized with 25 and 75% HEMA in the feed (Table I) using 0.5% AIBN at 60°C in N_2 atmosphere for 40 h. The polymer was precipitated in excess water, filtered, washed, and dried in vacuum at RT. The inherent viscosity of the polymer solutions was measured in DMF at 0.5% concentration at 30°C using an Ubblehode viscometer. The molecular weights of the polymers obtained were determined using GPC (Waters, U.S.A.) with styrogel 10^5, 10^4, and 10^3 Å columns in series using THF as the mobile phase at a flow rate of 1.5 mL/min. Polystyrene of three different narrow molecular weights was used as the standard with UV detector at 254 nm. The transition temperatures of the polymers were determined using a differential thermal analyser (DTA) (DuPont, 990) at a heating rate of 10°C in an atmosphere of air.

RESULTS AND DISCUSSION

The structure of the monomers IEH and TIPM follow.



(IEH)



(TIPM)

Table I Inherent Viscosity Values in DMF and Molecular Weights of Homopolymers of IEH and TIPM and Their Copolymers with HEMA

Polymer Composition	Inherent Viscosity (dL/g)	Molecular Weight
IEH (100%)	0.0342	8,000
IEH–HEMA (25:75 in feed)	0.0388	2,000
TIPM (100%)	0.0580	1,300
TIPM–HEMA (25:75 in feed)	0.2934	10,000

The monomer IEH, which is the esterification product of iothalamic acid with HEMA is a yellow powder soluble in methanol, ethanol, acetone, DMF, etc., but insoluble in hydrocarbon solvents. TIPM is a light yellow colored viscous liquid that was also soluble in similar polar organic solvents. In TLC, both monomers exhibited a single spot with ethyl acetate as the eluent. The R_f values were 0.76 for IEH and 0.70 for TIPM, respectively. The IR spectrum of TIPM showed a peak at 1770 cm^{-1} (ester) and at 1560 cm^{-1} ($c = c$) with the disappearance of the peak at 3460 cm^{-1} due to the phenolic group, which originally existed in the triiodophenol spectrum. Similarly, the monomer IEH showed the characteristic ester peak at 1780 cm^{-1} and the $c = c$ peak at 1620 cm^{-1}, which was broadened having coupled with the amide peak at 1650 cm^{-1}. The ^{1}H NMR spectra showed the characteristic peaks assigned as:

IEH: 5.7 and 6.0∂(CH_2)(singlets), 3.6 and 4.1∂ (—O—CH_2—CH_2—O—)(triplets), 2.4∂(C—CH_3), 2.9∂(N—CH_3)(singlets), 1.8∂(C—CH_3)(singlet). TIPM: 8.4∂(aromatic)(singlet), 5.8 and 6.3∂(=CH_2)(singlet), 1.25∂(=C—CH_3)(singlet).

The homopolymerization of the radiopaque monomers IEH and TIPM under the polymerization conditions employed failed to give high polymers. Instead, only oligomers were obtained as evidenced by the inherent viscosity values and the GPC analysis of the resulting polymers (Table I). Changing the initiator to BPO or BPO/*N,N*-dimethyl para toluidine redox system was also found to be of no use in obtaining polymers of high molecular weight. Copolymerization of the monomer HEMA with 25 wt % concentration of both radiopaque monomers in the feed also resulted in polymers with very low molecular weight as evidenced by their inherent viscosity values and GPC analysis. However, in the presence of 1–5 wt % concentration of a crosslinking

agent such as EGDM, TIPM up to 50 wt % concentration could be copolymerized with HEMA using AIBN as the catalyst resulting in a hard, yellow, transparent crosslinked polymer, which on equilibration with water turned cloudy due to the uptake of water by the PHEMA segments in the gel. But, IEH in concentrations of more than 25 wt % could not be copolymerized with HEMA even in the presence of EGDM as the polymerization did not go to completion even after several days. The resistance to polymerization could be due to the presence of the bulky iodine atoms in the monomer sterically hindering the propagation step.

The DTA spectra of the homopolymers of TIPM and IEH and their copolymers with HEMA showed the characteristic transition temperatures. While the DTA spectra of the copolymers exhibited sharp peaks of transition temperatures, the homopolymers showed several other transitions seen as noises in the spectra. The decomposition temperatures observed from endothermic peaks are given in Table II. The melting points were also confirmed by the capillary melting method. The melting occurred without further yellowing of the polymer confirming the stability of the iodine-containing polymers during melting.

Attempts to copolymerize the radiopaque monomers with MMA using AIBN or BPO also did not result in a high polymer. It was found that the polymerization reaction was inhibited by the presence of the bulky iodine-containing monomers. Possibly, under drastic conditions such as under high pressure, these monomers could be copolymerized with monomers such as MMA in reasonable concentrations (10–20%) to produce a high polymer, which will exhibit good radiopacity. However, this was not attempted in the present investigation.

As part of an ongoing program to prepare polymeric microspheres with radiopaque properties for therapeutic embolization, microspheres of the IEH–HEMA copolymer were prepared by the solvent evaporation method. The copolymer, prepared by polymerizing HEMA in the presence of 25 wt % IEH, was dissolved in 1 : 1 acetone–methanol to give a 20% solution. Of this solution 7.5 mL was mixed with 0.5 g of NaCl and was dispersed in a dispersion medium that consisted of 45 mL of liquid paraffin of 18 cps viscosity, 5 mL of *n*-heptane, and 0.1 g of dioctyl sulphosuccinate as the suspension stabilizer taken in a 150 mL beaker. Evaporation of the solvent at room temperature while the suspension was kept stirred at 100 rpm using a stainless steel paddle stirrer led to microspheres with more than 50 wt % of the fraction having diameter more than 1.00 mm. Washing out the NaCl after the microspheres were formed generated pores and channels in them, a condition that will favor the ingrowth of tissues when the spheres are implanted. Microspheres were also crosslinked by treating them with a 1% solution of hexamethylene diisocyanate in *n*-hexane at room temperature for 12 h. The crosslinking imparted better dimensional stability to the particles. Microspheres of varying size ranges (100–1500 μm) could be prepared by changing the viscosity of the dispersion medium, concentration of the stabilizer, the stirring speed, etc. The scanning electron micrograph (SEM) of the microspheres prepared by the solvent evaporation method is shown in Figure 1. Figure 2 shows the X-ray photograph of the microspheres demonstrating the excellent radiopaque nature of these particles. Microspheres of TIPM–HEMA copolymer could also be prepared in an identical manner.

Table II Thermal Transition Temperatures of the Homo and Copolymers of IEH and TIPM from DTA Analysis

Polymer Composition	T_m (°C)	T_d (°C)
IEH (100%)	165	305–330
IEH–HEMA (25 : 75 in feed)	125	290
TIPM (100%)	< 50	310
TIPM–HEMA (25 : 75 in feed)	125	305

As a preliminary test of biocompatibility of the copolymers of the radiopaque monomers with HEMA, microspheres of IEH–HEMA and TIPM–HEMA were tested for their potential to cause blood hemolysis using heparinized calf blood.[9] The data (Table III) indicate that the presence of triiodophenyl methacrylate containing copolymer is potentially hemolytic whereas the IEH-containing copolymer does not cause any blood hemolysis. Thus, it is reasonable to presume that polymers containing triiodophenyl methacrylate will not be suitable for any implant applications. On the other hand the IEH-based polymer may well be tolerated by the living tissue, a result not surprising because of the fact that iothalamic acid is a nontoxic diagnostic reagent used intravenously in interventional radiology.

CONCLUSIONS

Acrylic acid derivatives of iodine-containing compounds such as triiodophenol and iothalamic acid

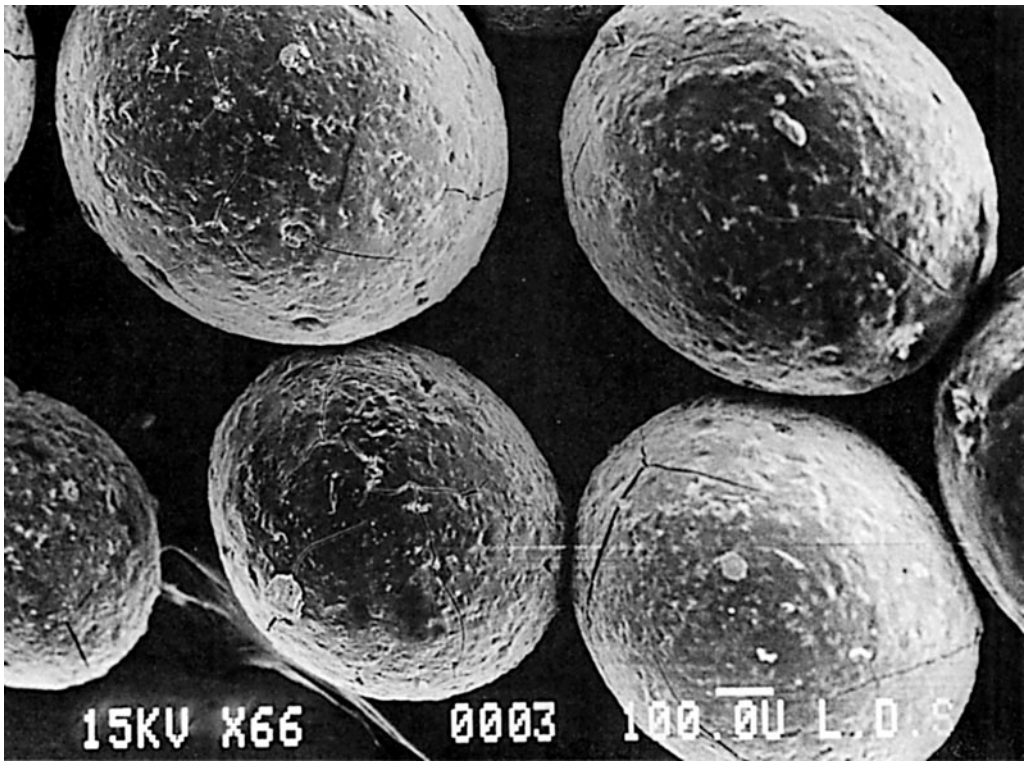


Figure 1 SEM of IEH–HEMA (25 : 75) copolymer microspheres.

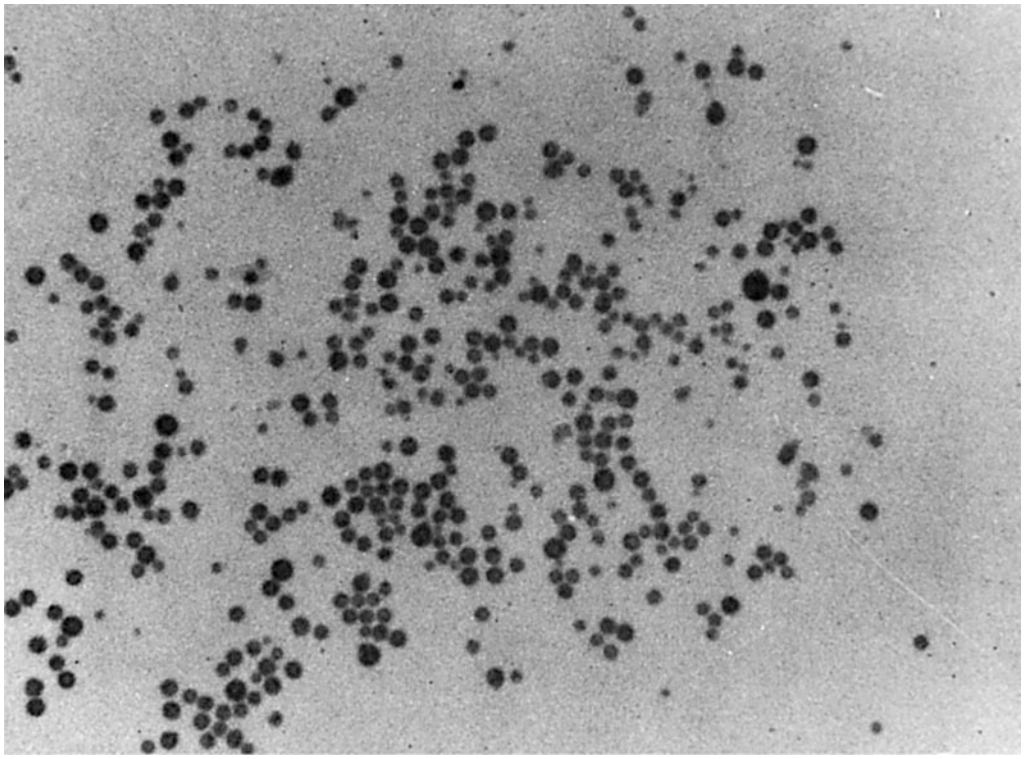


Figure 2 X-ray image of IEH–HEMA (25 : 75) copolymer microspheres.

Table III Amount of Plasma Hemoglobin Released in the Presence of Copolymer Microspheres

Material	Hemoglobin Released (mg %)
Control	18.4
IEH–HEMA (25 : 75)	19.7
TIPM–HEMA (25 : 75)	164.8

prepared with a view of producing radiopaque polymers for biomedical use were found to be highly resistant to homopolymerization and copolymerization with monomers such as HEMA and MMA under normal conditions by free radical initiators. Only oligomers could be obtained. However, the monomers in concentrations up to 25 wt % could be copolymerized with HEMA in the presence of small concentrations (1–5 wt %) of a crosslinking agent such as EGDM resulting in a hard, yellow transparent polymer. While triiodophenyl methacrylate based polymers were found to be hemolytic in nature, polymer based on iothalamic acid was found to be nonhemolytic in in vitro tests. Polymeric microspheres with radiocontrast properties could be prepared by solvent evaporation of the copolymers of IEH and TIPM with HEMA and crosslinking the microspheres using hexamethylene diisocyanate. Such microspheres may find application as radiopaque emboli in interventional radiology.

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