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Synthesis and characterization of iodinated polyurethane with inherent radiopacity

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ABSTRACT

The synthesis and characterization of polyurethane (PU) with excellent radiopacity for medical and allied applications are reported. Bisphenol-A (BPA) was iodinated to obtain 4,4′-isopropylidinedi-(2,6-diiodophenol) (IBPA) which was used as a chain extender for the preparation of a radiopaque PU. The PU was prepared by reacting 4,4′-methylenebis(phenyl isocyanate) (MDI), poly(tetramethylene glycol) (PTMG) and IBPA in 2.2:1.2:1 molecular ratio and is characterized by infrared spectroscopy (IR), thermogravimetry (TGA), dynamic mechanical analysis (DMA), energy dispersive X-ray analysis (EDX), gel permeation chromatography (GPC) and X-radiography. X-ray images showed that the PU prepared using IBPA as the chain extender is highly radiopaque. An *in vitro* cytotoxicity test using L929 mouse fibroblast cells shows that the PU is non-cytotoxic. The outlined synthesis of a PU with radiocontrast properties opens up the possibility of synthesizing many different kinds of radiopaque PUs with desirable range of physical properties exploiting the versatility in their chemical synthesis.

1. Introduction

Polymeric biomaterials having radiopacity are being used for medical applications such as cardiovascular implants, prostheses, orthopedic implants and controlled drug release devices since it allows post-operative assessment of the fate of the device using X-radiography [1]. Often these devices are made radiopaque by incorporating metal powder such as tantalum or metal salts of barium, bismuth, uranium into the systems [2,3]. Conventional polymers cannot be detected by X-ray and ultrasound because they contain elements such as C, H, O and N, which exhibit low electron density and low specific gravity. Hence, strategies to develop radiopaque polymers focus on ways to increase the average electron density and specific gravity of polymers.

The incompatibility of the above inorganic additives with polymer matrix often affects the physical and mechanical properties of the implants or prostheses adversely. Moreover, the possibility of inorganic ions leaching into the body fluid in the case of long term applications makes radiopacity a temporary phenomenon apart from producing systemic toxicity [4,5]. The second approach towards achieving radiopacity is to prepare radiopaque polymer–salt complexes. This method is popular for dental implants. But the ionic nature of these systems causes absorption of water leading to hydrolysis resulting in the loss of the radiopacifying atom [6,7].

Another approach to achieve radiopacity is to covalently attach a radiocontrast dye to the polymer. This method has been investigated for the preparation of radiopaque hydrogel beads by acylating poly(2-hydroxyethyl methacrylate) beads with triiodobenzoic acid, iothalamic acid and iopanoic acid [8,9] and for making cellulose radiopaque by coupling triiodobenzoic acid with the hydroxyl group of cellulose [10]. We recently reported on the modification of commercial PUs by coupling iodine-containing molecules onto the backbone of the polymer to render them radiopaque [11,12].

A better approach to make radiopaque polymers is to synthesize monomers having covalently bound heavy halogen atoms such as iodine or bromine and use these monomers as building blocks of new polymers that show intrinsic radiopacity [13–15]. Earlier studies employing this method mainly deal with vinyl polymers. Thus, iodine containing acrylates and methacrylates has been synthesized and their polymerization and copolymerization were studied with other acrylic monomers leading to good radiopacity for the resultant polymers [16–25]. Some recent literatures also reported the use of iodine containing poly(vinyl alcohol) based hydrogel and salicylate-based poly(anhydride–esters) as radiopaque biomaterial [26,27].

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Polyurethanes are an important class of biomaterials and it will be advantageous if they exhibit X-ray contrast properties in applications such as heart valves, catheters and vascular stents [12]. Radiopaque polyurethanes can be made by any of the general methods mentioned earlier. However, commercially available radiopaque polyurethanes are usually formulations which contain additives like barium sulphate, tungsten or bismuth salts and hence may exhibit the shortcomings associated with similar systems as mentioned above [4,5].

Disclosures on radiopaque polyurethanes, where the radiopacity arise due to the presence of iodo- or bromo- compounds can be found in the patent literature. Blends of polyurethanes with diiodo- or tetraiodo-benzoates [28,29] and fabrication of transparent radiopaque catheters from polyurethanes containing halogen moieties such as brominated glycols or diisocyanates have been disclosed [30,31]. Patent literature also deals with use of chain extenders like tetrabromodipentaerythritol, dibromopentyl glycol and tetrabromobisphenol-A-bis(2-hydroxyethyl ether) in the preparation of radiopaque polyurethane [32,33].

In this work we report the synthesis and characterization of (a) IBPA and (b) radiopaque polyurethane using IBPA as chain extender.

2. Materials and methods

2.1. Materials

Bisphenol-A (4,4′-isopropylidenediphenol) (BPA) (Sigma–Aldrich, MO, USA) was recrystallized from dry toluene before use. 4,4′-Methylenebis(phenyl isocyanate) (MDI) (Sigma–Aldrich, MO, USA) was used without further purification. Poly-(tetramethylene glycol) (PTMG) (Terathane 1000) (Sigma–Aldrich, MO, USA) was degassed for 24 h at 50 °C under reduced pressure. Sodium hypochlorite (approx 4% (wt/v) available chlorine) and sodium hydroxide were procured from S.D Fine Chemicals, Mumbai, India. Dibutyltin dilaurate (DBTL) (Sigma–Aldrich, MO, USA), dimethyl formamide (DMF) (S.D Fine Chemicals, Mumbai, India) were distilled under reduced pressure and kept over 4 Å molecular sieves.

2.2. Methods

2.2.1. Synthesis of 4,4′-isopropylidinedi(2,6-diiodophenol) (IBPA)

Iodination of BPA to synthesize IBPA was carried out according to the procedure reported by Kevin and Edgar for iodination of phenols [34]. BPA, 2.00 g (0.0087 mol) was dissolved in 50 mL of methanol. Six equivalents of sodium iodide (7.8 g, 0.052 mol) and 2 equiv of sodium hydroxide (0.69 g, 0.0176 mol) were added and the solution was cooled to 0 °C. Aqueous sodium hypochlorite (98.3 mL, 6 equiv, 0.052 mol of sodium hypochlorite) was then added dropwise over 75 min at 0–3 °C. As each drop hits the solution, a red color appeared and faded almost instantly, resulting in a yellow colored solution. It was stirred for 1 h at 0–2 °C and was then treated with 20 mL of 10% aqueous sodium thiosulphate and was precipitated by adding 10% HCl. A white solid was formed which was further washed with methanol to remove unreacted BPA, as BPA dissolves in methanol while IBPA does not.

2.2.2. Synthesis of polyurethanes

Polyurethane was prepared using MDI, PTMG with IBPA as chain extender. Polymerization was carried out by two-step process. MDI, PTMG and IBPA were used in the molar ratio of 2.2:1.2:1. MDI, 2.24 g (0.0089 mol) and PTMG, 4.86 g (0.0048 mol) were dissolved in DMF taken in a round bottom flask fitted with mechanical stirrer under nitrogen atmosphere, and kept at 90 °C for 4 h. DBTL (0.05 wt% of reactants) was added followed by the addition of 3 g (0.004 mol) of IBPA dissolved in 15 mL of DMF through a pressure-equalized addition funnel and the reaction was maintained at the same temperature under stirring for another 2 h. The reaction mixture was allowed to cool to room temperature and kept under stirring for another 18 h. Polyurethane (MTIB) was isolated by precipitation from cold water, which was further washed with methanol. The product was obtained in 90% yield. In a similar manner, polyurethane (MTB) was also prepared from the same reactants in the same molar ratio but using BPA as chain extender for comparative studies.

2.2.3. Characterization

Infrared (IR) spectra were recorded in a Fourier transform infrared (FTIR) instrument (Nicolet, Model Impact 410, Madison, WI). NMR spectra were recorded using a Bruker 300 MHz instrument (Bruker AC-300, USA) with TMS as the internal standard and DMSO d_6 as the solvent. Thermal analyses such as thermogravimetric

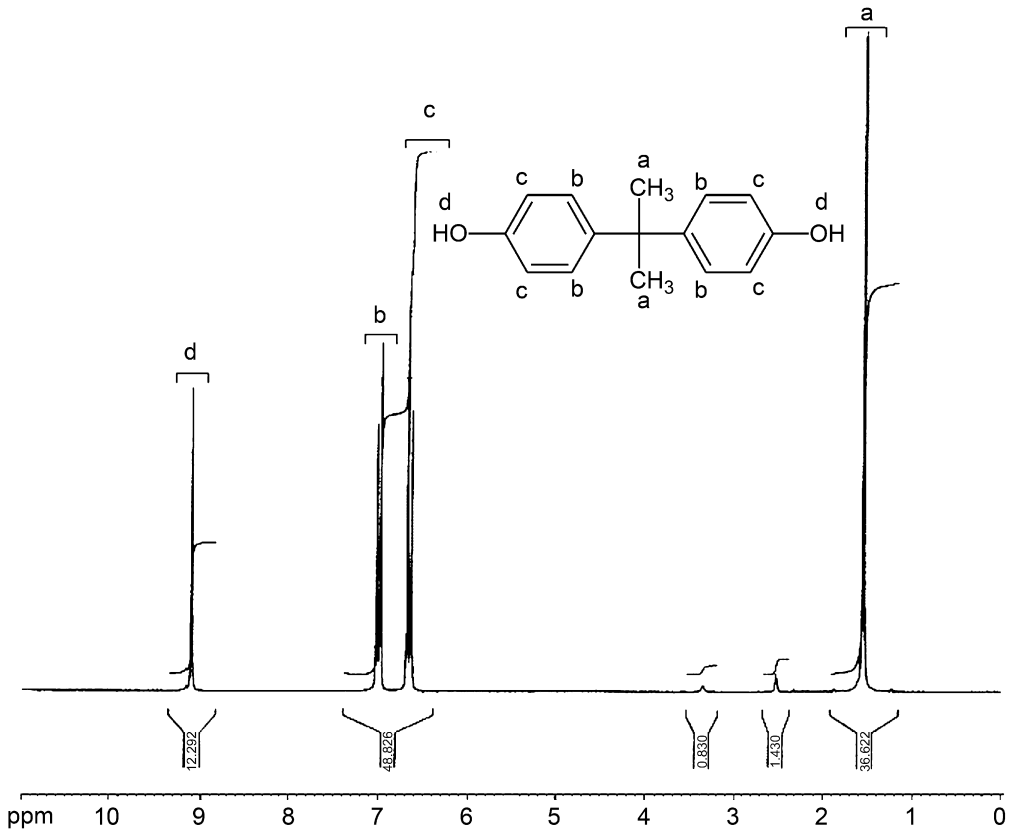

Fig. 1. ^{1}H NMR of BPA.