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Development of a hydrophobic polymer composition with improved biocompatibility for making foldable intraocular lenses

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ABSTRACT

A hydrophobic composition for foldable intraocular lenses was developed by copolymerizing phenyl ethyl acrylate, phenyl ethyl methacrylate and butanediol diacrylate by gamma irradiation. Aqueous solution of heparin, a biocompatibilizer absorbed in hydroxyethyl methacrylate was added to the monomer mixture before irradiation to impart desired level of hydrophilicity and improved biocompatibility to the hydrophobic composition. Ketorolac tromethamine, an anti-inflammatory agent and L-glutathione, an antioxidant were added to the composition as functional additive for exhibiting improved performance while in use. Concentrations of monomers, biocompatibilizer and functional additives were optimized to develop an advanced material for foldable intraocular lenses. Transmittance, refractive index, Abbe number, hardness, tensile strength, flexibility and foldability were studied on the final composition. Scanning electron microscopic study, differential scanning calorimetric analysis, leachability and viscometry confirmed the permanent incorporation of additives into the polymer. Results of haemocompatibility, tissue implantation and cytotoxicity confirm that the biocompatibility of the base polymer was improved by incorporation of heparin.

1. Introduction

Polymers have been extensively used in recent days to replace conventional materials for different uses especially for biomedical applications. High-tech polymers are used to create new and improved artificial limbs. Artificial knees and hips made up of specialty polymers provide people with trouble free joints and pain free movement. Today polymers address wide range of health care needs from petridishes in laboratory to bioresorbable coronary stents after heart surgery. The use of polymers in place of the metallic frames of spectacles and the glass lenses of eye-glasses has improved comfortability and safety of the people. Until 1970s a very thick glass, known as aphakic glass was used after cataract surgery to provide vision to the patient. The first intraocular lenses were made of glass, which were heavy and prone to shatter during Nd:YAG capsulactomy. Nowadays advanced polymeric materials have been used for making foldable intraocular lenses.

The use of plastic materials in ophthalmic applications, such as spectacle lenses, contact lenses and intraocular lenses (IOLs) has been the subject of interest for material scientists all over the world [1–7]. The advent of microsurgical techniques has revolutionized cataract surgery, where surgeons remove a cataractous lens through a much smaller incision (2.8–3.5 mm) as compared to conventional extra-capsular cataract removal techniques. This evolution would have not been completed without a lens that could be implanted through this significantly smaller incision. As a result, the idea of a foldable intraocular lens (IOL) has been conceived by the material scientists. A foldable IOL is made up of a plastic material that can be folded and implanted through a smaller incision of the above order. Aromatic polyacrylates and polymethacrylates are the material of choice for foldable IOL till today. Despite the excellent track record of more than fifty years, some postoperative complications associated with acrylic IOL still exist. Although acrylics are relatively inert with human tissues, the IOL made out of this polymer are not truly biocompatible while foreign body reactions are registered to cause intraocular inflammation along with a fibrinous uveitis after the surgery.

Heparin, one of the most common mucopolysaccharides is the natural component of mammalian cells and as such is not recognized as a foreign body by the mammalians. Hence, heparin, by definition, a biocompatible macromolecule when introduced into the body during a surgery, may be recognized as a normal constituent and undergoes the normal metabolic degradation of circulating heparin. Current scientific and clinical literature

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unequivocally demonstrates that the presence of heparin in synthetic intraocular lenses makes them more biocompatible and reduces the foreign body inflammatory reactions to a great extent. Attempts to improve the biocompatibility of IOLs have included the binding of heparin and hyaluronic acid to the outer surface of the lens [8]. The coatings of heparin and hyaluronic acid were shown to reduce protein adsorption, cellular adhesion and neutrophil activation by the PMMA surface and were shown in vivo to reduce cellular deposition onto the IOLs [9,10]. Lundgren et.al found reduced fibrin and membrane formation following implantation of heparin surface modified IOLs [11]. The reduced postoperative inflammatory reaction is indicative of the increased biocompatibility of the heparin surface modified IOLs [12–15]. The materials used to form these coatings may not be compatible with each other, thereby making it difficult to form a coating that is truly biocompatible. On the other hand, irradiation sources may be useful for activating the components of a coating composition, but can cause degradation of the bioactive agent that is present in the coating. Another problem is related to the release of bioactive agents; some materials release the bioactive agents immediately upon contact with tissue, as a result the bioactive agent may not be sufficient enough to provide a beneficial effect later [16].

The immobilization of heparin to biomaterials as well as applications of these heparinized biomaterials have been widely studied by many workers in recent days [17]. Immobilized heparin, unlike soluble heparin inhibits the initial contact activation coagulation enzymes through an antithrombin III mediated pathway, and thus show better anticoagulant properties [18]. Heparin conjugation to biomaterials was originally explored to reduce the thrombogenicity of materials in contact with blood. Recently heparin has been conjugated to biomaterials for drug delivery applications. More recently, the use of heparin as a base polymer for scaffold fabrication has also been explored, often utilizing non-covalent binding of heparin with peptides or proteins to promote self-assembly of hydrogel networks [19]. Heparin conjugated linear and star shaped polylactic acid to improve blood compatibility and its related biocompatibility of degradable polymers were studied by Park and coworkers [20]. Marconi et al. prepared biocompatible substances by immobilization of heparin to ethylene vinyl alcohol copolymer by covalent bonding [21]. Kang and co-workers prepared functional group grafted heparinized polyurethanes by employing plasma glow discharge [22]. Fabia and co-workers prepared heparinized polyethylene and hyaluronic acid immobilized polyethylene by employing plasma treatment in O_2/H_2O radio frequency glow discharges and plasma enhanced chemical vapour deposition fed with acrylic acid [23,24]. Immobilization of heparin or hyaluronic acid onto polyethylene substrates increased the Partial Thromboplastin Time (blood clotting time) to about 15 s, when the non-heparinized (or hyaluronic acid) substances had a clotting time of only 10 s. This demonstrates that the anticoagulant property of heparin/hyaluronic acid was preserved on polyethylene substrate.

In this work we have discussed about the development of an advanced material for making foldable IOL mainly to enhance its biocompatibility by incorporating heparin, the most common bioactive material into the base polymer of a combination of acrylic monomers. Free radical polymerization of the acrylic monomers mixed up with heparin was carried out by irradiation of lower doses of gamma rays for the preparation of the said biocompatible material. The problem associated with the instability of heparin in the polymer surface is thus expected to be eliminated by the bulk incorporation of this biomolecule into the polymer matrix.

2. Material and methods

2.1. Materials

2-Hydroxyethyl methacrylate (HEMA), 1,4-butanediol diacrylate (BDDA), 2-Phenyl ethyl acrylate (PEA) and 2-Phenyl ethyl methacrylate (PEMA) were used as monomer in this study. Sodium salt of heparin as biocompatibilizer, ketorolac tromethamine as anti-inflammatory agent and glutathione reduced as antioxidant were used as functional additives. The details of all the raw materials are given in Table 1.

2.2. Methods

2.2.1. Preparation of IOL material

PEA, PEMA, HEMA and BDDA were taken in a prefixed ratio in a glass mold. An aqueous solution of sodium salt of heparin, ketorolac tromethamine and glutathione reduced in different concentrations was added to the monomer mixture followed by gamma irradiation at a predetermined dose to obtain the polymer to be used as IOL material. Optimization of different parameters at various steps involved in the preparation of the resulting polymer is narrated in the following sections.

2.2.2. Optimization of dose of gamma irradiation

PEA and PEMA (1:1, w/w) were taken in glass molds and irradiated at different doses: 10, 20, 30, 40 and 50 kGy of gamma rays. In practice polymer sheets were cast by injecting the monomer mixture into the mold followed by polymerization by gamma irradiation. The optimum dose was determined by comparing various properties of the resulting polymers. The optimized dose to produce the polymer of desired characteristics was 30 kGy.

2.2.3. Optimization of monomer ratio

Different proportions (w/w) of PEA and PEMA were taken, namely, PEA: PEMA (0:1), (1:2), (1:1), (2:1) and (1:0), in glass molds and polymerized at the optimum radiation dose. The polymers were evaluated for different physico-mechanical properties and the best composition was found to be PEA: PEMA (2:1).

2.2.4. Optimization of co-monomer

Optimized concentration of PEA: PEMA (2:1) was taken with different concentrations (w/w) of BDDA (0%), (3%), (6%), (10%)]

Table 1
Materials.

Materials used	Grade	Source	Features
2-Hydroxyethyl methacrylate (HEMA)	Laboratory reagent	Acros organics	97% Pure
1,4-Butanediol diacrylate (BDDA)	Laboratory reagent	Sigma–Aldrich	90% Pure
2-Phenyl ethyl acrylate (PEA)	Laboratory reagent	Polysciences, Inc.	B.P. 104–106 °C
2-Phenyl ethyl methacrylate (PEMA)	Laboratory reagent	Polysciences, Inc.	B.P. 119–120 °C
Heparin sodium	Laboratory reagent	CDH	100,000 IU/vial
Ketorolac tromethamine	Laboratory reagent	Sigma–Aldrich	376. 4 g/mol
L-glutathione reduced	Laboratory reagent	Sigma–Aldrich	307. 3 g/mol
HPLC water	Laboratory reagent	Merk	pH 5–8