Polypropylene fumarate/phloroglucinol triglycidyl methacrylate blend for use as partially biodegradable orthopaedic cement

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Abstract

Polypropylene fumarate/phloroglucinol triglycidyl methacrylate oligomeric blend-based bone cement was studied. Higher the percentage of phloroglucinol triglycidyl methacrylate, lesser the setting time. An optimum setting time could be arrived with 50:50 blend composition of the two oligomers. Composite cement of 50:50 blend prepared with hydroxyapatite granules of particle size 125 μm binds bovine rib bones. The tensile strength of this adhesive bond was found to be 1.11 kPa. The thermal studies suggest the onset of cross-linking reaction in the cured blend if the blend is heated. The absence of softening endotherm in the cured blend shows the thermosetting-like amorphous nature of blend system, which may restrict the changes in creep properties. The in vitro biodegradation studies reveal possible association of calcium ions with negatively charged units of degrading polymer chain resulting in slow down of degradation. Relatively slow degradation was observed in Ringer’s solution. The study reveals the potential use of polypropylene fumarate/phloroglucinol triglycidyl methacrylate as partially degradable polymeric cement for orthopaedic applications.

Keywords: Polypropylene fumarate; Phloroglucinol triglycidyl methacrylate; Bone cement; Orthopaedic applications

1. Introduction

Biodegradable bone cements that would provide immediate structural support and accelerate normal bone healing and remodelling process have potential orthopaedic and maxillofacial applications such as temporary stabilization for bone in-growth prostheses and augmentation of fracture fixation especially when the underlying bone stock is deficient or osteoporotic [1]. Tri calcium phosphate (TCP) and hydroxyapatite (HA) have been used as alternatives to bone grafts in the filling of skeletal defect [2]. These materials are considered as osteoconductive and non-osteoinductive [3]. Attempts have been made to alleviate this problem using composites of these particulate and compounds such as plaster of Paris, fresh blood and polylactic acid [4]. The idea of using polymers as binders for particulate ceramics to produce composites with improved handling properties and to overcome the problem of brittleness associated with ceramic bone implants has been studied by Bonfield et al. [5]. Poly(ε-hydroxy) acids, mainly lactide and glycolide homo- and copolymer are being the first choice among other biodegradable materials in the preparation of biomaterials for hard tissue repair [6–10]. Such composites are in effect biodegradable bone cements though their utility depends on the physical, mechanical and biological properties. Sandner et al. [11] have studied the polymerization shrinkage of composite resins and evaluated the working time of composite resins.

For orthopaedic and maxillofacial applications, it is suggested that biodegradable bone cement should meet certain criteria [12]. It must behave like cement that can be molded, shaped or injected into certain complex internal cavities in bone and harden in situ and develop mechanical properties sufficient to permit functional loading of the region. Bone cement must be biodegradable so that it does not act as a barrier to bone remodelling or fracture healing, but rather is replaced by host bone over a period of time. For orthopaedic applications, a synthetic, biodegradable and injectable oligomer, which can crosslink into hard material in vivo would be

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more useful for correcting osseous defects and inducing bone regeneration. Biodegradable poly(propylene fumarate) (PPF), its copolymers and composites have been studied as promising biomaterials for bone tissue engineering [13-15].

PPF was synthesized through different methods by various research groups. Sanderson [16] has prepared PPF as powder by a trans-esterification reaction between diethyl fumarate and propylene glycol in the presence of an acid catalyst, p-toluene sulphonie acid by heating to 250°C over a period of 5 h and vacuum drying at 220°C for 4 h. Gerhard and Hayes [17] have synthesized low molecular weight PPF (M_n = 500–1200, polymerization index (PI) = 3–4) by the condensation reaction between propylene glycol and fumaric acid by heating to 145°C for 5 h and then to 180°C. Gresser et al. [18] produced PPF (M_n=2600, PI-2.6) by the reaction of fumaric acid and propylene glycol using p-toluene sulphonic acid catalyst and i-butyl hydroquinone. Domb et al. [19] has prepared PPF by the reaction between propylene glycol and fumaric acid at 130°C for 10 h and then at 180°C for 2 h to get a viscous liquid with molecular weight (M_n) of 300–2000 and PI of 1.5–1.7. Domb et al. [20] have also prepared PPF by another two steps process. Initially, trimeric bis(2-hydroxy propyl fumarate) (HPF) was prepared by the reaction of propylene glycol and mixture of fumaric acid and pyridine in acetone. Then, propylene bis (hydrogen maleate) (PHM) was prepared by the reaction of propylene glycol and maleic anhydride in toluene at 100°C for 24 h. The intermediate product PPF (M_n-750, PI-2.4) was then prepared by melt condensation of HPF and PHM at 140°C for 24 h. Domb et al. [20] have introduced various terminal groups (acylate and epoxy) in PPF to study the degree of crosslinking and mechanical properties of the composite without crosslinking monomer. Yaszemski et al. [21] and Peter et al. [22] also have produced PPF (M_n-850, PI-2.0) by two step process. Initially, bis(2-hydroxy propyl fumarate) was prepared by the reaction of fumaryl chloride and propylene glycol at room temperature. The trans-esterification was carried out at 160°C for 24 h under vacuum with antimony trioxide catalyst. Szmeresanyi et al. [23] and Andreis [24] have prepared PPF through the condensation reaction between maleic anhydride and propylene glycol and studied the isomerization of maleate to fumarate groups. The synthesis of PPF by all these methods require careful implementation of polymerization conditions since the condensation reaction is an equilibrium reaction and the liberated by-product should be removed. The molecular weight of the PPF is limited by the reversible polyesterrification and trans-esterification reactions proceeding in temperatures above 180–200°C for several hours. Moreover, the condensation reaction at 190°C also involves cyclization side reaction involving the maleic anhydride and glycols which reduces the unsaturation (about 10–20%). However, the condensation reaction carried out at lower temperature enables only partial isomerization of maleate to fumarate groups. In order to get low molecular weight PPF with highly reactive and more planar trans-fumarate configuration, a meticulous synthetic procedure is needed.

Polypropylene fumarate based unsaturated prepolymer could be further polymerized in situ through crosslinking of double bonds with unsaturated monomers. The mechanical strength and biodegradation of the bone cement in vivo dependent on the main chain groups, end groups, co-reactants and crosslink density. As part of the development of biodegradable and injectable bone cement for orthopaedic applications, diethylene glycol acrylate-n-vinyl pyrrolidone copolymer resin [25] and poly(propylene fumarate-co-ethylene glycol) based bone cements were prepared and reported earlier [26]. Combination of epoxy group and acrylic and fumarate groups can offer a convenient route to a combination of thermosetting and thermoplastic properties. By crosslinking an epoxy acrylate and polypropylene fumarate oligomers a quite complex cured product that may have improved creep properties in vivo could be obtained. The cement should not undergo creep changes due to the effect of body temperature and or mechanical stress before the onset of degradation and bone growth. The present work also aims at possible development of bone cement which can set into a hard mass without the use of generally used fast activating amine accelerator, N, N dimethyl aniline and N, N dimethyl p-toluidine, etc. It has been found that these tertiary amines have been found to be toxic and mutagenic in host [27]. Therefore, the objective of the present paper is to develop and evaluate blends of polypropylene fumarate/phloroglucinol triglycidyl methacrylate as partially biodegradable and injectable bone cement for orthopaedic applications.

2. Materials and methods

2.1. Preparation of resins

Polypropylene fumarate (PF1) was prepared using maleic anhydride and 1,2-propylene glycol in presence of p-toluene sulphonie acid catalyst as reported elsewhere [28]. The second component phloroglucinol triglycidyl methacrylate (PA2) was also prepared and reported [29]. In short, phloroglucinol triglycidyl ether was prepared initially using phloroglucinol, epichlorohydrin, benzyl triethyl ammonium chloride and alcoholic sodium hydroxide. Then it was reacted with methacrylic acid in the presence of triethylamine catalyst. The residual triethylamine was not removed from the final oligomeric resin PA2. The residual tertiary amine acts as a moderate activating amine for the crosslinking of PA2 and PF1.
2.2. characterization of bone cement components

2.2.1. Determination of acid number

The acid constituent in the resins PF$_1$ and PA$_2$ was determined by finding the acid number as per ASTM standard D 2849. One gram of the resin was dissolved in benzene/ethyl alcohol mixture (1:1 v/v) and titrated against 0.1 M alcoholic KOH using phenolphthalein indicator. A blank titration was also carried out. The quantity of KOH required to neutralize acidic constituents in 1 g of resin was calculated as the acid number. Acid number = [(A – B)v x 56.1]/w, where ‘A’ and ‘B’ are the volume of KOH solution required for titration of the blank and test sample, respectively.

2.2.2. Infrared spectral studies of PF$_1$ and PA$_2$

The IR spectrum of PF$_1$ was recorded using a Nicolet (Impact 410) FT-IR instrument was used.

2.3. Preparation of blends of polypropylene fumarate/ phloroglucinol triglycidyl methacrylate acrylate (PF$_1$/PA$_2$)

A series of blends of varying compositions of PF$_1$ and PA$_2$ were prepared with and without HA. Blends of PF$_1$:PA$_2$ compositions 25:75, 50:50 and 75:25 were coded as PF$_1$/PA$_2$–A, PF$_1$/PA$_2$–B and PF$_1$/PA$_2$–C, respectively. The initiator benzoyl peroxide (3.75%) was added to initiate crosslinking of PF$_1$ and PA$_2$. Blends of PF$_1$ : PA$_2$ having composition 50:50 were prepared with hydroxyapatite [Ca$_{10}$(PO$_4$)$_6$(OH)$_2$] as filler. Blends with filler HA content 2.5%, 5.0% and 10% were coded as PF$_1$/PA$_2$–D, PF$_1$/PA$_2$–E and PF$_1$/PA$_2$–F, respectively (Table 1).

2.4. Characterization of bone cement

2.4.1. Determination of setting time

The setting time of adhesive blend composites with and without HA was determined as per ISO 5833/1-1999 E Standard. The components were mixed thoroughly in presence of initiator benzoyl peroxide at 37°C and the time taken for curing the blend to solid mass was determined. The average temperature was determined by taking half the sum of ambient temperature and exothermic setting temperature. The time taken to reach the average temperature was found as setting time.

2.4.2. Studies of adhesive bonding of bones using PF$_1$/PA$_2$/HA

Bovine rib bones were procured from the slaughter house, cleaned well with isotonic saline solution, removed adhering muscles and fixed in 10% formaldehyde solution for 3 days. The bone samples were washed well with distilled water, and dried in oven at 60°C. The bone cement composite of PF$_1$/PA$_2$/HA (125 μm) were applied to bone joints as soon as the initiator was added and blended well with the mixture. The bonded bone joints were subjected to tensile tests as per ASTM standard as reported earlier [26]. Tensile strength was found by using an Instron Corporation, series IX automated materials testing system 743.00 at a crosshead speed of 5 mm/min.

2.5. Studies on cured bone cement blends

2.5.1. Thermal studies of cured bone cement blends

The thermal behaviour of the cured blends was determined by thermogravimetric (TG) and differential thermal analysis (DTA). The samples were heated at 10°C to a maximum temperature of 500°C in nitrogen atmosphere using a universal VI-12 ETA thermal analyzer.

2.5.2. Studies on degradation of cured bone cement

The accelerated hydrolytic degradation of the polymers was studied by in vitro aging in various media such as phosphate buffered saline (PBS) and Ringer’s solution [30]. Disodium hydrogen phosphate 0.2 M (28.4 g of anhydrous Na$_2$HPO$_4$ per 1000 ml) and 0.2 M sodium dihydrogen phosphate (27.6 g of NaH$_2$PO$_4$ · H$_2$O per 1000 ml) in 0.9% saline solutions were prepared separately and mixed in the ratio 77:23 (v/v) such that pH would be 7.4. Ringer’s solution (pH = 8.4) was prepared by dissolving sodium chloride (9 g), sodium hydrogen carbonate (0.42 g), calcium chloride (0.24 g) and glucose (1 g) in 1000 ml distilled water. Uniform pieces of cured bone cement blend composites were accurately weighed and immersed in different media. The accelerated aging was carried out at 70°C for 30 days. Every 5 days interval, the samples were taken out, dried and weight loss was determined. The weight loss (%) was plotted against duration of exposure and the relative aging stability was determined.

3. Results and discussion

3.1. Materials

Acrylic bone cements have been used for orthopaedic applications as two-part component [31]. The major

Table 1

<table>
<thead>
<tr>
<th>Cement</th>
<th>PF$_1$ (g)</th>
<th>PA$_2$ (g)</th>
<th>Initiator (g)</th>
<th>HA (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF$_1$/PA$_2$–A</td>
<td>0.6</td>
<td>0.2</td>
<td>0.03</td>
<td>—</td>
</tr>
<tr>
<td>PF$_1$/PA$_2$–B</td>
<td>0.2</td>
<td>0.6</td>
<td>0.03</td>
<td>—</td>
</tr>
<tr>
<td>PF$_1$/PA$_2$–C</td>
<td>0.4</td>
<td>0.4</td>
<td>0.03</td>
<td>—</td>
</tr>
<tr>
<td>PF$_1$/PA$_2$–D</td>
<td>0.8</td>
<td>0.8</td>
<td>0.06</td>
<td>0.04</td>
</tr>
<tr>
<td>PF$_1$/PA$_2$–E</td>
<td>0.8</td>
<td>0.8</td>
<td>0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>PF$_1$/PA$_2$–F</td>
<td>0.8</td>
<td>0.8</td>
<td>0.06</td>
<td>0.16</td>
</tr>
</tbody>
</table>
disadvantages associated with acrylic cements are high exothermic heat, shrinkage, and allergic and toxic reactions of unreacted monomers, residual initiator and accelerator, and loosening of bone-implant interface [32]. Modifications of acrylic bone cements were attempted with hydroxy ethyl methacrylate, ethylene glycol dimethacrylate and ultrahigh molecular weight polyethylene though limited in success [33]. Bisphenol A glycidyl methacrylate-bonding agent is in routine use for dental cement composite [34]. Poly(propylene fumarate) has been studied as biodegradable material for tissue engineering and orthopaedic applications. However, polypropylene fumarate-phloroglucinol triglycidyl methacrylate blends system could be a better combination giving fast setting, adhesive bonding and controlled biodegradability. Both polypropylene fumarate (PF1) and phloroglucinol triglycidyl methacrylate (PA2) are oligomeric viscous liquids [28,29]. The molecular structures of blend components are given in Scheme 1. Hydroxyapatite was prepared [35] and supplied as 125 μm size granules from Bioceramics Division, SCTIMST.

3.2. Characterization of cement components PF1 and PA2

The infrared spectrum of the oligomer phloroglucinol triglycidyl methacrylate (PA2) is given in Fig. 1. The appearance of a strong peak at 1725.15 cm⁻¹ indicates the ester group of acrylate. The presence of -OH group in the resin is also indicated with the peaks at 1409.79 and 3431.41 cm⁻¹. The aromatic ring of phloroglucinol is seen with sharp peak at 1599.74 cm⁻¹. The residual epoxide group of resin is observed with the peak at 1295.33 cm⁻¹. The IR spectral responses of polypropylene fumarate (PF1) reveal presence of unsaturation (C=C) in fumarate unit at 1643.32 cm⁻¹ and ester (C=O) unit at 1741.13 cm⁻¹ (Fig. 1). The peaks around 2983 and 2944 cm⁻¹ are due to aliphatic (C–H) groups in the two spectra. The more intense peak at 3499.13 cm⁻¹ indicates PF1 has more hydroxyl end groups suggesting the liquid resin in the oligomeric form. The acid value of oligomers PF1 and PA2 are 156.519 and 51.612, respectively. This indicates that PF1 resin is end capped with acid group whereas PA2 is end capped with both acid and hydroxyl units.

3.3. Preparation and characterization of blends of cement

Determination of setting time revealed the extent of the fast crosslinking reaction between the unsaturated double bonds of PF1 and PA2. The data of setting time for blends of PF1 and PA2 are given in Table 2 and Fig. 2. The curve A represents the setting PF1 and PA2 without HA. Lesser the percentage of PF1 and the higher the percentage of PA2, the lower is the setting time. The crosslinking reaction of PF1 and PA2 resulted in a crosslinked product comprising of PF1 and PA2 in a random fashion (Scheme 2). The crosslinking took place through C=C bond of PF1 and PA2 as the IR spectrum of crosslinked polypropylene fumarate showed absence of peak around 1644 cm⁻¹ and around 982 cm⁻¹ (due to –C–H bending of –CH=CH– of units) as reported earlier [26]. The slow crosslinking reaction in blends having higher percentage of PF1 is attributed to the presence of maleate ester in PF1 in addition to fumarate units. The maleate units were less reactive than vinyl, acrylic, and fumarate units [34]. The setting characteristics of blends of PF1 and PA2 with HA are given Table 2 and curve

Scheme 1. Structure of blend components — phloroglucinol triglycidyl methacrylate (PA2) and polypropylene fumarate (PF1).
B of Fig. 2. The HA content has an important role in the setting reaction. An optimum amount (5%) of HA gave lower setting in comparison with the composition having the lowest and highest amount of HA. The basicity of HA influenced the setting reaction. Blend having 2.5% HA may be more acidic and that with 10% HA may be more basic, which hinders crosslinking. Therefore, an optimum 5% HA enabled the polymer composite to have comparatively lower setting time.

3.4. Determination of adhesive bonding strength in bone

Bone cement comprising PF₁ (47.06 ppm), PA₂ (47.06 ppm), benzoyl peroxide (3.53 ppm) and HA (2.35 ppm) were blended and used for bonding bovine rib bones. The tensile test data revealed that the adhesive bonding has strength 1.11 kPa and low percentage strain. The toughness was found to be 0.0688 kPa, which indicated that the bonded bone cement is brittle in nature.

3.5. Thermal studies of cured bone cement

The thermal studies revealed the degree of curing in a cured product as well as the thermal stability of the cured product. The data on differential thermal analyses of the cured bone cement with and without HA filler are given in Table 3. The DTA curves of bone cement without HA showed two mild transitions at 55°C and 102°C. These peaks were somewhat well defined in the case of PF₁/PA₂–A, which could be due to the presence of homopolymers by the polymerization of PA₂ and PF₁ in the blend. The high setting time (230 min) also supported this possibility. The DTA curve of PF₁/PA₂–A showed exothermic peak at 124.65°C which was due to the crosslinking reaction between the remaining PF₁ and PA₂ components (Table 2). PF₁/PA₂–B exhibited the exothermic peak at 118.91°C, which could be due to individual crosslinking of PA₂ due to the presence of higher quantity of fast reactive phloroglucinol component. The lesser area under this peak for PF₁/PA₂–B

<table>
<thead>
<tr>
<th>Cement</th>
<th>Setting time at 37°C (min)</th>
<th>Crosslinking temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF₁/PA₂–A</td>
<td>230</td>
<td>124.65</td>
</tr>
<tr>
<td>PF₁/PA₂–B</td>
<td>21</td>
<td>118.91</td>
</tr>
<tr>
<td>PF₁/PA₂–C</td>
<td>40</td>
<td>138.26</td>
</tr>
<tr>
<td>PF₁/PA₂–D</td>
<td>133</td>
<td>130.36</td>
</tr>
<tr>
<td>PF₁/PA₂–E</td>
<td>101</td>
<td>129.95</td>
</tr>
<tr>
<td>PF₁/PA₂–F</td>
<td>240</td>
<td>122.03</td>
</tr>
</tbody>
</table>

*From DTA analyses.
Fig. 2. Setting characteristics of bone cement blends.

Table 3
Thermal decomposition characteristics of cured bone cement blends

<table>
<thead>
<tr>
<th>Blend system</th>
<th>Temperature (°C) at weight loss</th>
<th>Decomposition temperatures (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10%</td>
<td>50%</td>
</tr>
<tr>
<td>PF_1/PA_2−C</td>
<td>210</td>
<td>370</td>
</tr>
<tr>
<td>PF_1/PA_2−B</td>
<td>240</td>
<td>350</td>
</tr>
<tr>
<td>PF_1/PA_2−C</td>
<td>230</td>
<td>360</td>
</tr>
<tr>
<td>PF_1/PA_2−D</td>
<td>250</td>
<td>375</td>
</tr>
<tr>
<td>PF_1/PA_2−E</td>
<td>230</td>
<td>380</td>
</tr>
<tr>
<td>PF_1/PA_2−F</td>
<td>225</td>
<td>390</td>
</tr>
</tbody>
</table>

*From TGA curves.
*From DTA curves.

Unlike PF_1/PA_2−A also indicated the lesser degree of individual crosslinking reaction. The lower temperature transitions were not clear in bone cements with filler. This may be due to the absence of higher quantities of individual homopolymer. The exothermic peak for crosslinking reactions also appeared as mild in the HA filled bone cement. Comparing the DTA curves of PF_1/PA_2−C (without HA) and PF_1/PA_2−D (with HA), a small exothermic peak appeared at 130.36 °C for the latter. However, PF_1/PA_2−F exhibited a well-defined exothermic peak at 122.03 °C for crosslinking which indicated slow speed of crosslinking reaction in the presence of higher amount of HA. There was no clear melting endothermic peak in DTA curves, owing to the thermosetting-like amorphous nature of blend components. The decomposition peak for the highest decomposition temperature (T_d1 or T_d2) of unfilled and filled cured bone cement.

Scheme 2. Crosslinked structure of PF_1/PA_2 blend.
3.6. Studies on in vitro biodegradation

A biodegradable bone-filling material should be degraded about the same rate of the new bone tissue formation. The profile of accelerated hydrolytic degradation in vitro media is shown in Figs. 3 and 4. The weight loss during aging clearly indicated the hydrolytic degradation of cured bone cements. The pH (7.4) of the solution decreased appreciably especially in PBS medium and reached a constant value (Table 4). This revealed degradation and association of calcium ions with negatively charged units of PF$_1$ and PA$_2$ backbone. This acted as a buffer and arrested further lowering of pH. This ionic association slowed down the hydrolytic degradation after an initial period of 17 days. The higher decrease of pH (≥ 40%) observed in PBS media than in Ringer’s solution (≥ 20%) suggested higher degree of ionic association in Ringer’s solution than in PBS. Therefore, more degradation was noticed in PBS medium (Figs. 3 and 4). After 30 days of aging more than 50% of degradation was observed. HA granules can neutralize the acidic degradation products of polyester and further reduce the auto-catalytic degradation of the polymer phase. The studies revealed that the present bone cement was partially biodegradable having proper degradation rate that would degrade the polymer matrix within 2–3 months.

4. Conclusion

Studies on polypropylene fumarate/phloroglucinol triglycidyl methacrylate oligomeric blend have revealed...
that the blend composition influences the setting polymerization reaction in the presence of free radical catalyst (benzoyl peroxide) at 37°C. The higher the percentage of phloroglucinol triglycidyl methacrylate the lesser the setting time. An optimum setting time could be arrived with 50:50 blend composition of the two oligomers. Addition of HA increases the setting time of the blend. Though aromatic amine activator could be used to reduce the setting time further, it is wise to avoid and use safe formulation. Composite cement of 50:50 blends prepared with HA granules of particle size 125 μm bind bovine rib bones. The tensile strength of this adhesive bond was found to be 1.11 kPa. The toughness and elongation data suggested that the cured cement is brittle in nature due to insufficient macromolecular chain growth. The thermal studies suggest the onset of crosslinking reaction in the cured blends if the blend is heated. The absence of melting endotherm shows the thermosetting-like amorphous nature of blend system, which can resist changes in creep properties. The in vitro biodegradation studies of HA added blends reveal possible association of calcium ions with negatively charged units of degrading polymer chain resulting slow down of degradation. Relatively slow degradation was observed in Ringer’s solution. The study revealed the potential use of polypropylene fumarate/phloroglucinol triglycidyl methacrylate as an in situ polymerizable, injectable and partially biodegradable orthopaedic cement.

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