

# Chemical characterization of a degradable polymeric bone adhesive containing hydrolysable fillers and interpretation of anomalous mechanical properties

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## Abstract

An experimental, light-curable, degradable polyester-based bone adhesive reinforced with phosphate glass particles ( $(\text{P}_2\text{O}_5)_{0.45}(\text{CaO})_x(\text{Na}_2\text{O})_{0.55-x}$ ,  $x = 0.3$  or  $0.4$  mol) or calcium phosphate (monocalcium phosphate/ $\beta$ -tricalcium phosphate (MCPM/ $\beta$ -TCP)) has been characterized. Early water sorption (8 wt.% at 1 week) by the unfilled set adhesive catalysed subsequent bulk degradation (4 wt.% at 2 weeks) and substantial decline in both elastic and storage moduli. Addition of phosphate glass fillers substantially enhanced this water sorption, catalysed greater bulk mass loss (40–50 and 52–55 wt.%, respectively) but enabled generation of a microporous scaffold within 2 weeks. The high levels of acidic polymer degradation products (38–50 wt.% of original polymer) were advantageously buffered by the filler, which initially released primarily sodium trimetaphosphate ( $\text{P}_3\text{O}_9^{3-}$ ). Calcium phosphate addition raised polymer water sorption to a lesser extent (16 wt.%) and promoted intermediate early bulk mass loss (12 wt.%) but simultaneous anomalous increase in modulus. This was attributed to MCPM reacting with absorbed water and  $\beta$ -TCP to form more homogeneously dispersed brushite ( $\text{CaHPO}_4$ ) throughout the polymer. Between 2 and 10 weeks, linear erosion of both polymer ( $0.5$  wt.% week<sup>-1</sup>) and composites ( $0.7$ – $1.2$  wt.% week<sup>-1</sup>) occurred, with all fillers providing long-term buffer action through calcium and orthophosphate ( $\text{PO}_4^{3-}$ ) release. In conclusion, both fillers can raise degradation of bone adhesives whilst simultaneously providing the buffering action and ions required for new bone formation. Through control of water sorption catalysed filler reactions, porous structures for cell support or substantially stiffer materials may be generated.

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## 1. Introduction

There is a vast need for injectable, rapidly setting adhesives/cements for bone tissue-engineering and maxillofa-

cial/orthopaedic applications [1]. Currently, no commercialized bone repair product is ideal. Conventional injectable polymethacrylate-based bone cements, for example, are non-degradable. This raises concern about their long-term biocompatibility [2,3]. Also, calcium phosphate cements (hydroxyapatite-forming versions) have a slow setting reaction which may affect their stability in blood or tissue fluid. Moreover, the set materials have low mechanical properties [4–6] and, due to limited aqueous solubility, are not readily converted to new bone in vivo. More soluble brushite-forming versions, containing tricalcium phosphate, set much faster [7–9] but their early instability

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in aqueous fluids remains a matter of concern as with any hydrophilic or water-based formulation.

More recently, alternative hydrophobic, injectable, light-curable and degradable polypropylene fumarates [10,11], polyanhydrides [12,13] and short-chain polyesters end capped with methacrylate groups suitable for bone fixation have been formulated [14–17]. This study focuses upon a dimethacrylate polyester adhesive [16,17] that sets rapidly via light-activated polymerization. The degradation of the set material is a complex process and appears to be a combination of early water sorption catalysed bulk degradation (which may seriously affect mechanical properties) followed by surface erosion.

With degradable polymers, higher degradation rates often correlate with greater hydrophilicity of the polymer and hence water sorption [15–17]. Higher degradation rate would also cause more acid accumulation and potential inflammatory response in vivo. Fillers that could increase the degradation kinetics of a hydrophobic formulation and release calcium and phosphate to facilitate more rapid replacement with new bone, but simultaneously increase adhesive mechanical properties and buffer the acid production, could therefore be of significant benefit [18,19]. Hydroxyapatite [13,20,21] and/or  $\beta$ -tricalcium phosphate fillers [11,22] can improve various mechanical properties of polymers but their low aqueous solubility only provides a limited buffering capacity [19]. They also tend to reduce polyester water sorption and thereby degradation kinetics [20–22]. Conversely, phosphate glasses can be produced with wide-ranging degradability/solubility [23–24]. These have been used previously for reinforcing various polymers [25,26] but may also be drawn into fibres. Such fibres, upon degradation within a polymer, could potentially form channels within the composite, increasing the chance for vascularization and nutrition diffusion [27].

Therefore in this study, dimethacrylate polyesters reinforced with either phosphate glasses of different compositions in particulate form or calcium phosphate (a combination of both high-solubility monocalcium phosphate (MCPM,  $(\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O})$ ) and low-solubility  $\beta$ -tricalcium phosphate ( $\beta$ -TCP,  $\text{Ca}_3(\text{PO}_4)_2$ ) fillers were investigated. The aim was to assess if it is possible to control water sorption of this hydrophobic polymer with the benefit of increased ion release and polymer degradation but simultaneously improve mechanical properties such as modulus and buffer acidic polymer degradation products.

The objectives were:

- (i) To study the effect of these fillers on setting polymerization kinetics.
- (ii) To gain better understanding of any chemical change of both fillers within these degradable polymers and correlate it with any variation in mechanical and pH buffering characteristics.
- (iii) To examine the calcium and phosphate ion (essential in the bone repair process) release capacity of these adhesives.

- (iv) To test the hypothesis that MCPM will promote water sorption, and in the presence of  $\beta$ -TCP will bind this water, forming brushite ( $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ ). This ion-exchange/precipitation process occurs in brushite cements [8,9] but has not previously been observed directly within a polymer catalysed by water sorption.
- (v) To quantify this ion-exchange/precipitation reaction and its effects on polymer degradation and mechanical properties.

## 2. Materials and methods

### 2.1. Sample preparation

#### 2.1.1. Poly(lactide-co-propylene glycol-co-lactide) dimethacrylate oligomeric monomer

The oligomeric monomer synthesis, purification and characterization are described in detail elsewhere [16]. Briefly, polypropylene glycol (PPG, molecular weight  $1000 \text{ g mol}^{-1}$ , Aldrich) was reacted with D,L lactide ( $\text{C}_6\text{H}_8\text{O}_4$ , Aldrich) at a molar ratio of 1:4 in the presence of stannous octoate (0.05% (w/w) of PPG) that was added as catalyst. The reaction occurred under vacuum and a nitrogen atmosphere at  $150^\circ\text{C}$  for 6 h. The resultant intermediate triblock poly(lactide-co-propylene glycol-co-lactide) was then dissolved in dichloromethane. Methacrylate groups were subsequently attached through reaction at  $0^\circ\text{C}$  with triethylamine, and methacryloyl chloride each at 4 mol per mol of intermediate. Finally, triethylamine hydrochloride was precipitated and removed through repeated acetone addition, filtration and drying.

#### 2.1.2. Phosphate glass

Preparation and characterization of  $(\text{P}_2\text{O}_5)_{0.45}(\text{CaO})_x(\text{Na}_2\text{O})_{0.55-x}$  ( $x = 0.3$  or  $0.4$  mol) has been reported in numerous previous studies [23–26]. Briefly sodium dihydrogen orthophosphate ( $\text{NaH}_2\text{PO}_4$ ), calcium carbonate ( $\text{CaCO}_3$ ) and diphosphorous pentoxide ( $\text{P}_2\text{O}_5$ ) (BDH, UK) were heated in a furnace (Carbolite, RHF 1600, UK) initially at  $300^\circ\text{C}$  for 30 min, then at  $600^\circ\text{C}$  for 30 min and finally at  $1050^\circ\text{C}$  for 1 h. The resultant glass was quenched to room temperature, ground and sieved to obtain a particle size in the range of 20–45  $\mu\text{m}$ .

#### 2.1.3. Mixed MCPM/ $\beta$ -TCP filler

The calcium phosphate mixture used consisted of equimolar sintered  $\beta$ -TCP of  $\sim 62 \mu\text{m}$  and MCPM of  $\sim 11 \mu\text{m}$  size.

#### 2.1.4. Composite formulations

For polymer and composite formulations, the oligomeric monomer was combined with 10 wt.% hydroxyethyl-methacrylate (HEMA; Sigma–Aldrich) and 1 wt.% each of camphorquinone (CQ) and *N,N*-dimethyl-*p*-toluidine (DMPT; Sigma–Aldrich). The filler/oligomeric monomer

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