

Compaction strategies for modifying the drug delivery capabilities of gelled calcium polyphosphate matrices

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Abstract

Calcium polyphosphates (CPPs) have shown potential as drug delivery matrices, particularly in treating bone-related chronic diseases such as osteomyelitis, where maintenance of sufficient bactericidal concentrations at the infected bone site is essential. The objective of this study was to incorporate an additional compaction step as part of a gelling protocol to optimize CPP matrix properties while enhancing their drug delivery capabilities. Vancomycin-loaded CPP powders were produced using a previously established gelling and drying protocol (G1), and then subsequently compacted at prescribed levels (30, 113 or 452 MPa) before subjecting to an additional gelling and drying protocol (G2). The resulting G2 disks were found to be more homogeneous and dense ($p = 0.0013$) when compared with corresponding G1 disks, though increases in matrix density did not translate into subsequent increases in tensile strength. The compaction regelling protocol did, however, eliminate the burst release phenomena observed with the G1 disks and further extended the release of vancomycin into a clinically acceptable therapeutic range of 3 weeks. These changes were associated with the increase in visual homogeneity, the increase in density and a more homogenous dispersion of vancomycin within the G2 disks. The ability to modulate this release profile to a limited extent by altering compaction stress, particle size distribution and regelling time was also demonstrated. Overall, the compaction regelling protocol described here, when used in conjunction with an initial gelling step to achieve matrix drug loading, enhances the flexibility and long-term drug delivery capability of this CPP matrix.

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1. Introduction

Osteomyelitis is a significant, difficult-to-treat disease, denoting the inflammation of bone and marrow usually caused by pyogenic bacteria. With an annual incidence of 2% in the USA, osteomyelitis results in substantial health-care costs and disability [1]. The initiation of systemic antibiotics, drainage of purulent loci and debridement of necrotic tissue is the current standard therapy for osteomyelitis [2]. However, a major problem with this approach lies in obtaining bactericidal concentrations of therapeutic agents at the area of infection [3]. Other drawbacks include

system toxicity, where non-targeted organs are affected, and the unreliable penetration into ischaemic tissue by the therapeutic agent [4].

A number of local drug delivery systems have been developed, each with varying degrees of success or shortcomings, to achieve local concentrations higher than the minimum inhibitory concentration (MIC) without producing dangerous systemic levels [5–11]. At minimum, these delivery systems are required to carry and provide the timely release of an appropriate therapeutic dosage while not disrupting the effectiveness of the drug. However, there is also a desire to avoid additional surgery for matrix retrieval while also addressing the often substantial bone loss resulting from the infection and subsequent debridement procedures. Ideally, then, these systems should also be

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osteoconductive and non-immunogenic to facilitate bone growth, while degrading at a rate complementary to that growth [11–16]. For load-bearing applications, there will be the additional need to sustain loads comparable to those typically associated with cancellous bone (2–20 MPa).

The potential of osteoconductive calcium polyphosphates (CPPs) $[\text{Ca}(\text{PO}_3)_2]_n$ to incorporate and maintain a TA within a degradable matrix has been explored in previous work by our group [17–19]. Here, a reproducible gelling protocol that takes advantage of the unique hygroscopic nature of calcium polyphosphates was established that allows for incorporation of an antibiotic within the CPP matrix without disrupting its functionality [17]. Drug incorporation was also shown to have a minimal effect on the gelling process, with neither chain length nor matrix tensile strength being significantly altered [17]. It was initially postulated that interparticle bonding and gelling, which was previously observed in calcium polyphosphates exposed to a highly humid environment [20], could contribute to a greater control over the release of entrapped therapeutic and resorption of the matrices in vitro. The mechanisms surrounding this gelling process are not well understood and are currently the subject of rigorous characterization studies. However, it is considered to be to some extent a limited degradation process involving solvation/hydrolysis, with a subsequent condensation reaction upon drying to yield an altered, though still identifiable, polyphosphate structure around the dissolved TA [17,18].

In initial drug delivery studies using vancomycin (VM), Dion et al. [18] showed that this gelling protocol, with subsequent drying, significantly reduced the rate of antibiotic release during the first 2–4 h of elution while extending the effective release period by 80 h compared with non-gelled samples. Initial swelling followed by the erosion of the inner core of the matrices suggested that the main degradation process associated with therapeutic release was bulk erosion. No correlation was found between the dissolution of calcium or phosphate from the matrices and VM released, implying that the release of the associated therapeutic was not governed solely by diffusion or bulk erosion but rather by a complex interaction of the two processes [18].

Despite the advances made with this system, some issues limiting their practical application remain. This novel gelling procedure led to an inconsistent pore distribution throughout the condensed matrices, decreasing the tensile strength of the matrices as the gelling time increased [17]. The observed non-uniformity of the disks likely contributed also to a reduced but still present “burst” release and the insufficient effective release time, believed to be of the order of 2–4 weeks.

These findings and limitations are the impetus behind this current work. To meet the ongoing challenges of developing a degradable, osteoconductive therapeutic delivery system for the treatment of osteomyelitis, a number of powder compaction processes were considered to augment

what was effectively a matrix (drug) loading step. Several compaction approaches exist, some of which have already been explored for calcium phosphate drug delivery vehicles [21–30]. Little, however, has been done with the relatively straightforward uniaxial compression or pelleting approach common in the pharmaceutical industry [31,32].

The key objectives of this study were to (i) develop a compaction-gelling procedure in conjunction with an initial drug loading gelling step to enhance both the physical properties of the delivery matrix and its drug delivery behaviour and (ii) demonstrate an ability to modulate in vitro delivery profiles through strategic selection of compaction processing parameters.

2. Materials and methods

2.1. Condensed calcium polyphosphate powder production

Calcium phosphate monobasic monohydrate crystals ($\text{Ca}[\text{H}_2\text{PO}_4]_2 \cdot \text{H}_2\text{O}$) were calcined at 500 °C in a platinum–5% gold crucible for 10 h, subsequently melted at 1100 °C for 1.5–2 h to allow polyphosphate chain growth and then quickly quenched in deionized distilled water to obtain an amorphous calcium polyphosphate frit [33,34]. The resulting frit was washed three times with anhydrous ethyl alcohol and left to dry overnight under vacuum. The frit was then ground in 1 min intervals using a Fritsch Planetary Micro Mill with alumina mortars and balls. The resulting powder was classified using an Octagon Digital sieve shaker mounted with Laboratory Test Sieves to isolate <45 µm particles. The larger particles were remilled until all of the starting CPP powder was less than 45 µm in size [17].

2.2. Gelling protocol (G1)

Antibiotic loading of the CPP was achieved using a previously established gelling protocol [17,18]. Briefly, a VM–H₂O solution was combined with CPP powder (<45 µm) in the ratio 150 mg CPP:0.0602 ml distilled H₂O:7.5 mg VM within the finger tip of the nitrile glove to facilitate hand-mixing while ensuring minimal loss of the therapeutic. The resulting paste was transferred into disk-shaped polyvinylsiloxane molds until flush with the top surface, and then placed in a sealed vessel maintained at 37 °C and ~100% relative humidity for 5 h. This time was previously shown to effectively reduce the VM release rate from these matrices [18]. Once the “gelling” process was complete, the samples were left to dry within the incubator at 37 °C in atmospheric air for a minimum of 24 h. Drying was completed once the standard deviations in weight loss were less than 1% of the total sample weight [35].

2.3. Compaction regelling protocol (G2)

Following drying, the G1 disks were ground using a Fritsch Planetary Micro Mill with alumina mortars and

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