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Drug impregnation for laser sintered poly(methyl methacrylate) biocomposites using supercritical carbon dioxide

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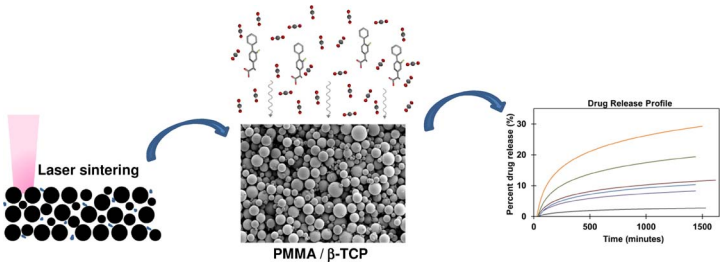
GRAPHICAL ABSTRACT



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ABSTRACT

Multi-functional biocomposites were developed using a 3D-printing method coupled with supercritical carbon dioxide ($scCO_2$) processing. Selective laser sintering was used to prepare poly(methyl methacrylate)/β-tricalcium phosphate biocomposites, which were subsequently treated with an anti-inflammatory drug (flurbiprofen) in $scCO_2$. Drug impregnation behaviors were investigated under different temperatures and pressures (313 K and 323 K; 85–115 bar). Results show that drug molecules were able to diffuse into the biocomposite structure effectively, achieving > 26% by weight of drug uptake. Surface morphology of the materials remained unaffected upon pro-longed $scCO_2$ processing. Drug release data was modeled using the Weibull function, indicating potential influences of $scCO_2$ processing temperature on the PMMA surface and the interaction between flurbiprofen particles and PMMA matrix inside the composite structure.

1. Introduction

In recent years, the rapid evolution of biomaterial processing has greatly expanded the functional diversity of composite products. A variety of polymeric materials have been developed, both biodegradable and biostable, for utilization as dental and orthopedic replacement devices, anti-microbial bone cements, as well as 3D scaffolding networks capable of promoting new tissue formation, amongst other applications [1]. Commanding increased attention, especially amongst pharmaceutical companies, is the potential use of biocomposite materials as controlled drug release systems (CRDS) [2,3]. CRDS involve biomaterials internally and externally infused with various anti-biotic/anti-inflammatory pharmaceuticals and have been tested to treat infections such as osteomyelitis and ophthalmic inflammation associated with surgical procedures [4,5].

Poly(methyl methacrylate) (or PMMA), an acrylic, hydrophobic,

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biostable polymer, has been identified in the literature as a highly suitable vessel for local drug delivery due to its excellent compatibility with human tissue and existing use for medical implants [6]. In addition, the fully amorphous structure and thermo-plasticity of PMMA allow for enhanced control over product dimensions and homogeneity of the overall structure [7,8]. The drug release profile of PMMA bone cements and other commercial PMMA-based devices depend on the porosity, surface extension, initial drug concentration, and thermostability of the compound [9]. Of elevated significance is the effect of inherent porosity of the polymer matrix; enhanced porosity is correlated with increased penetration of dissolution fluids into the matrix, thus resulting in higher quantities of drug elution from the device into the body [10,11].

To achieve higher internal porosity structure, PMMA-based composites enriched with β–tricalcium phosphate (β-TCP) are being investigated [11]. β-TCP is a biocompatible, osteo-conductive, porous ceramic commonly used as a bone substitute [6]. It invokes a unique biological response during bone remodeling in which the resorption of old bone minerals and formation of new bone occur simultaneously. During this process, the degraded calcium and phosphate ions are naturally metabolized, increasing the biodegradability of the ceramic [12]. In this way, PMMA/β-TCP biocomposites are able to maintain mechanical stability while simultaneously providing partial biodegradable character to mediate the release of bioactive drug molecules.

In this study, PMMA/β-TCP biocomposites were prepared using the most appropriate and powder-based 3D-printing method, the selective laser sintering (SLS) technique, for potential use as a polymeric CRDS as previously developed by Velu and Singamneni [7]. SLS allows researchers and practitioners to have theoretically unlimited control and freedom over product customization and *meso*- or macrostructures, including interconnected porosity. In SLS, a CO_2 laser is typically used to melt the polymer particles and sinter them into the desired 3D form from the bottom up, one layer at a time. To form the biocomposite, the ceramic powders are premixed with selected polymer particles before printing. The ceramic powders act as the functional, bioactive agent embedded within the polymer matrix. The ceramic phase also reinforces the polymer matrix and influences the overall strength of the biocomposite [13]. This novel biocomposite preparation method maintains structural integrity of the composite as well as homogeneity of the pores, which is essential for even drug distribution within the biomaterial.

To further enhance the composite and give it the multi-functional property, supercritical carbon dioxide ($scCO_2$) was used to impregnate an anti-inflammatory drug, in this case flurbiprofen, into the PMMA/β-TCP composite structure. CO_2 is a common greenhouse gas, with relatively low critical temperature and pressure (T_c = 304 K, P_c = 73.8 bar). In supercritical state, CO_2 can act as a non-toxic solvent to chemical compounds that are normally insoluble in liquid CO_2. For example, many anti-inflammatory drugs, such as triflusal, ketoprofen, piroxicam, nimesulide and flurbiprofen, have been shown to exhibit reasonable solubility in $scCO_2$ within 303–323 K temperature range [14–16]. $ScCO_2$ can also act as a carrier to transport material from one phase to another. It has been used widely as a benign medium to enhance material properties, especially in polymers and composites [17–19]. Utilization of $scCO_2$ not only eliminates the need for toxic organic solvents but also has the potential to recycle the greenhouse gas back into the process as a closed-loop system. Moreover, this method lowers the risk of leaving residual toxic solvents inside the materials, and prevents thermal tension induced during the material formation process by conventional methods [20].

Evidently, 3D-printing methods allow building biocomposites of controlled porosity, while $scCO_2$ processing is effective in terms of loading and dissipation of drugs. A suitable combination of the two techniques can be envisioned as an innovative and effective means of achieving enhanced drug delivery systems. This study aims at such a solution, coupling selective laser sintering of biocomposite powders together with the $scCO_2$ processing for drug infusion and delivery. Flurbiprofen, an anti-inflamatory drug, was selected due to its favorable solubility in $scCO_2$ without the use of additional co-solvents [16]. It is also compatible with PMMA-based copolymers, especially those prepared by traditional polymerization method [4]. The behavior of flurbiprofen in solutions during the impregnation process and the drug release process was characterized by UV/vis spectroscopy. Drug release profile was analyzed and surface morphology of the treated biocomposites was examined for any impact of $scCO_2$ processing on the material.

2. Materials and methods

2.1. Materials

Poly(methyl methacrylate) (or PMMA) was purchased from Aldrich in powder form, with average particle size of 75 μm, melting and glass transition temperatures of 433 K and 379 K, respectively, and theoretical density of 1180 kg/m^3. β-Tricalcium phosphate (or β-TCP, $Ca_3(PO_4)_2$) powders were also purchased from Aldrich, with average particle diameter of 5 μm and molecular weight of 310.18 g/mol. Flurbiprofen ($C_{15}H_{13}FO_2$, CAS 5104-49-4) was obtained from Sigma in white powder form, with melting point range of 383–385 K, and used as is without further purification. ACS reagent-grade liquid ethanol (Arcos Organics, CAS 64-17-5) with purity of 99.5% was used as the solvent for drug dissolution. USP medical grade carbon dioxide, purchased from Airgas with > 99.9% purity, was used in all $scCO_2$ treatments.

2.2. Sample preparation

The laser sintering experimental setup developed by Velu and Singamneni [7] was used to print the specimens. The test setup used a CO_2 laser of 10.5-μm wavelength, which allowed higher absorptivity with most polymeric materials, including PMMA. Laser sintering results of PMMA and β-TCP previously reported by Velu and Singamneni [13] were used to identify the best composition and process parameter settings for the current experiments. Based on previous coalescence and porosity data, the 95% PMMA + 5% β-TCP composition was selected for the current work, with energy density of the laser set at 0.15 J/mm^2. A laser power of 38 W and scan speed at 450 mm/s allowed to achieve this energy density and the consolidation of the PMMA/β-TCP composites to the best possible extent. The samples were sintered with five layers each, and approximately 10 mm × 20 mm in size. Some samples were cut in two halves using sharp scissors prior to $scCO_2$ processing whereas some others were processed as a whole piece. The pre-sintered thickness of the spread powder was around 50–60 μm, which was finally reduced to approximately 30–40 μm due to further interaction with the laser energy input. The porosity of the sintered samples was estimated to be at around 50%, based on the evaluation of SEM images.

2.3. Supercritical carbon dioxide processing

Supercritical CO_2 (or $scCO_2$) processing of PMMA/β-TCP biocomposite samples was performed in 316-stainless steel cells (volume of 53–60 mL), equipped with calcium fluoride windows for *in situ* UV/vis spectroscopic monitoring. The experimental setup is similar to the $scCO_2$ processing setup previously reported by Ngo et al. [21]. Bicomposite samples were first loaded into the cell for each experiment. One experimental run (313 K and 85 bar) was performed on PMMA/β-TCP sample with $scCO_2$ only and in absence of flurbiprofen, to study the effect of $scCO_2$ alone on the biocomposite surface morphology. The remaining experiments were performed in presence of flurbiprofen. The amount of flurbiprofen used for each experiment was calculated to be at least three times the solubility limits of the drug under each pressure and temperature condition. This was to ensure excess drug availability for absorption into PMMA/β-TCP biocomposite samples during