PMMA Bone Cement-Based Chemotherapeutic Depot Enables Refilling For Customized Treatment Of Bone Cancer

Erika L. Cyphert, Nithya Kanagasegar, Ningjing Zhang, Greg D. Learn, Horst A. von Recum
Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, 44106

Statement of Purpose: Standard chemotherapy for bone tumors typically involves systemic administration of chemotherapeutic drugs, such as doxorubicin (DOX). However, non-targeted delivery increases dose requirements and results in off-target toxicity and suboptimal chemotherapeutic efficacy. Ineffective chemotherapy may necessitate substantial resection of tissues and or/total amputation. To reduce off-target toxicities associated with prolonged systemic administration of chemotherapeutics to treat primary bone tumors a variety of localized site-specific delivery systems have been developed. Nevertheless, there are currently no bone tumor chemotherapeutic delivery systems capable of providing long-term controlled and localized release that can be refilled on-demand and in a patient-customized manner. The objective of this work was to develop a proof-of-concept poly(methyl methacrylate) (PMMA) composite system for controlled delivery of DOX comprised of different amounts of insoluble γ-cyclodextrin (γ-CD) microparticles.

Methods: Insoluble γ-CD microparticles with and without DOX were added to Simplex HV radiopaque bone cement (Stryker) powder prior to polymerization in ratios of 5, 10, and 15wt% (weight of microparticles to weight of PMMA powder). PMMA composite dough was either punched into small beads (6 mm diameter) or placed in cylindrical molds (12 mm height x 6 mm diameter). Micro-computed tomography (micro-CT) scans were performed to assess porosity of PMMA samples with DOX and DOX-filled γ-CD microparticles. To evaluate the impact of additives (free DOX and DOX-filled γ-CD microparticles) on the mechanical properties of PMMA composites, uniaxial compression tests were carried out. To evaluate the ability of PMMA containing γ-CD microparticles to be refilled with DOX following implantation in tissue, an agarose-based tissue-mimicking refilling model was used and drug loading capacity was quantified by dissolving PMMA beads in dimethyl sulfoxide to leach out DOX [1]. Release kinetics of DOX from different PMMA compositions were evaluated at discrete time points in PBS under infinite sink conditions. To ensure that the amount of DOX released from prefilled PMMA composites was therapeutically sufficient to eradicate osteosarcoma tumor cells (MG-63) over time, MTS cytotoxicity studies were completed.

Results: The ultimate compressive strength of the PMMA composites was inversely related to the average pore volume (correlation coefficient = -0.74). Therefore, PMMA composites with a larger average pore volume (PMMA/15wt%CD-DOX) resulted in weaker mechanical strength. Nevertheless, PMMA/CD-DOX composites continued to strengthen over time and surpassed the necessary 70 MPa threshold to be used for fixation of internal orthopaedic prostheses. As the content of CD microparticles in PMMA increased, there was an increase in the amount of DOX refilled qualitatively (**Figure 1a.**) and quantitatively. Refilled PMMA/15wt%CD composites released nearly 3 times the cumulative amount of DOX than any of the other composites (**Figure 1b.**) and demonstrated a consistent and prolonged release over 74 days. The cumulative amount of DOX released from PMMA/15wt%CD at 7 and 14 days significantly outperformed the cytotoxicity of aliquots from PMMA with free DOX (no CD) against MG-63 cells. A localized, refillable DOX delivery system is highly advantageous for effective treatment of bone tumors. It offers patient customization while simultaneously providing long-lasting therapy. Future work could explore incorporation of combinatorial chemotherapeutics into PMMA composites to improve therapeutic outcomes against primary osteosarcoma tumors.

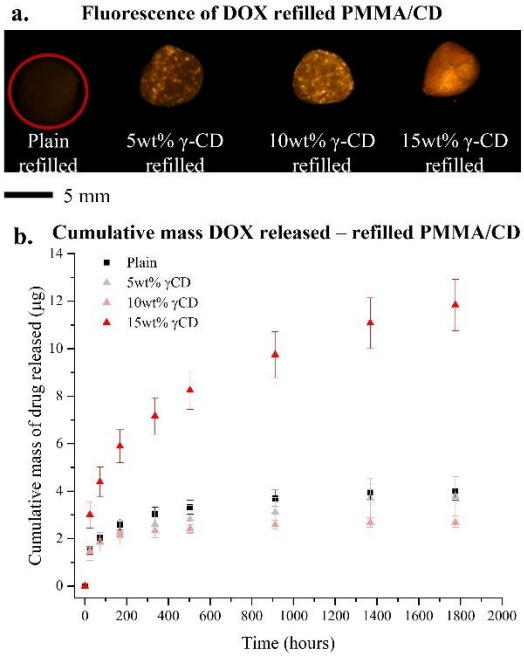

Figure 1. (a) DOX fluorescence intensity in PMMA/CD (correlated to refilling capacity) increased with the amount of γ-CD. **(b)** PMMA/15wt%CD refilled with DOX demonstrated consistent release over 74 days.

References: [1] Cyphert et al. *Adv Healthc Mater* 2018;7:1800812

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