Monitoring Degradation of Implantable Drug Delivery Devices using MR Relaxation & Diffusion Imaging

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Introduction: A modern approach to the treatment of chronic bone infection (osteomyelitis) involves implantation of a drug-loaded bioceramic material for localized delivery of therapeutic agents. Furthermore, bioceramics that are degradable offer considerable advantages over non-degradable ones, as they require no surgery for removal, and the very mechanisms of degradation may even be exploited to control the rate of release[1,2]. Amorphous calcium polyphosphate (CPP) is a polymer-like bioceramic under consideration for just such an application. In light of the dynamic interplay between degradation and release in CPP, MRI microscopy is invaluable as a non-destructive tool for characterizing (and eventually optimizing) this material for use in drug delivery applications.

In previous work[3,4], the imbibed fluid density and the T_1 relaxation time were mapped over time in CPP disks. The current study expands on this with measurement of both T_1 and T_2 relaxation times as well as the apparent diffusion coefficient (ADC). These parameters offer both direct and indirect measures of the mobility of imbibed fluid, which is ultimately responsible for drug transport.

Methods: CPP disks (4 mm diameter, 2 mm thick) were fabricated using gelling and gelling-compaction protocols, referred to as G1 and G2, respectively. The resulting disks are known to have different physical and chemical microstructures, and elution studies have revealed important differences in their drug release characteristics[5, 6]. For imaging, the disks were fixed in close-fitting NMR tubes using cyanoacrylate glue and then immersed in phosphate buffered saline (PBS) at physiological pH. Images were acquired at times ranging from 1 hour to 13 days post-immersion.

One-dimensional MR images were acquired on an 11.7 T magnet and a Bruker Avance spectrometer with a 5 mm ^{1}H probe and 707 mT/m triple-axis imaging gradients. Maps of T_1 and T_2 relaxation times were acquired using inversion recovery and CPMG sequences, respectively, and maps of the ADC were acquired using a pulsed-gradient stimulated echo (PGSTE) sequence. Least-squares regression was used to acquire the relaxation/diffusion parameters, and all relaxation/diffusion-weighted images were acquired with 256 points at 35 µm resolution.

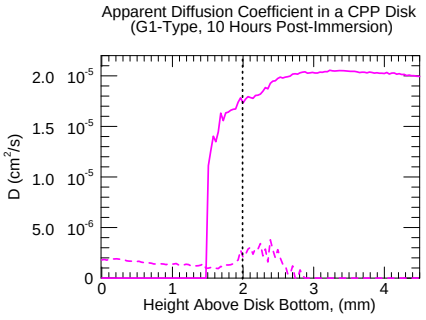

Fig. 1: Biexponential regions may be found in all parameter maps, such as the one between 1.5 and 3.0 mm in this map of the ADC in a G1 disk. The solid line is the longer component and the dashed line is the shorter one. The horizontal axis represents height, with zero at the bottom of the disk, and the original disk height shown by the dotted line.

Results & Discussion: The T_1, T_2, and the ADC maps contained many similarities, which is expected because all three parameters are indicators of the motion of imbibed water molecules. In particular, the maps have in common that at certain times and in certain regions of the disks, the relaxation and diffusion constants contain two components ("biexponential") instead of just one ("monoexponential"). An example of this is shown in Figure 1.

Biexponential components have previously been observed in maps of T_1, and it has been hypothesized that there are at least two environments for water in CPP disks, with slow exchange between them[3]. It is thought that these include water closely associated with CPP chains and water freely diffusing in open spaces within the bioceramic matrix. The ADC measurements (a direct and quantitative measure of molecular motion) confirm this hypothesis, with the restricted environment having an ADC of about 0.2×10^{-5} cm^2/s, and the other environment having an ADC between this and the value for free water (2.2×10^{-5} cm^2/s). Regions of the disk with monoexponential relaxation/diffusion may still contain both environments; however, if open spaces are small enough that exchange between the two environments is rapid, then only one component will be observed. The appearance and growth of a second exponential component is thus evidence for growth of the free-water regions.

In addition to the appearance of the "free-water" component, the relative weighting of that component increases over time. This is shown in Figure 2 for the T_2 relaxation time in G1 and G2 disks, and indicates that, gradually, a greater percentage of imbibed water occupies the more open elements of the physical microstructure. Interestingly, the major difference between the G1 and G2 disks is the time frame over which this change occurs. It is suspected that this is related to the changing release rates that have been previously observed in the two different materials.

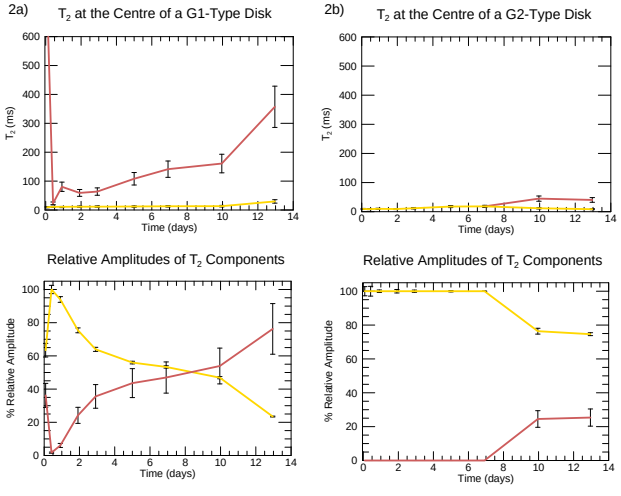

Fig. 2: Time evolution of the T_2 relaxation components and their relative amplitudes at the centre of a) a G1 disk and b) a G2 disk. The long component is shown in maroon and the short component in gold.

Conclusions: MRI microscopy has been used to map the T_1, T_2, and ADC in CPP disks, and has demonstrated sensitivity to differences in the microstructure of the two different types of disk. The ADC, in particular, is a direct measure of water transport that confirms the existence of both slow- and fast-diffusing water components. These components, along with their changing relative weighting, provide support for a mechanistic interpretation for observed transitions between Fickian and non-Fickian diffusion that is responsible for the delayed drug release in G2 disks. Future work will include simultaneous MRI and drug elution measurements, which will reveal definitively how changes in the CPP microstructure affect elution rates. This, in turn, will guide selection of processing parameters for fabrication of optimally-effective medical materials.

References:

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