MR Microscopy Can Resolve Differences in the Behaviour of Implantable Drug Delivery Biomaterials

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Introduction

While novel and innovative interventions in regenerative medicine hold great promise, such methods are only as effective as the ability to develop an empirical and mechanistic understanding of how/why they work. One such example is the use of resorbable bioceramics, which have potential to provide large, sustained concentrations of therapeutic agents to a specific tissue, while not exceeding the minimum toxic concentration in other tissues.

Optimization of resorbable bioceramic design requires methods that will permit the non-invasive and non-destructive study of the spatially and temporally varying physicochemical changes that occur due to material degradation. The study of drug delivery biomaterials using MRI therefore has the potential to significantly improve the understanding of the performance of such devices.

The current study focuses on the use of MR imaging and relaxometry to characterize the spatial-temporal evolution of amorphous Calcium Polyphosphate (CPP) bioceramics, intended for implantation into bone fractures for treatment of osteomyelitis. The ability of MR microscopy to resolve changes in the internal network will be demonstrated by comparing the results obtained as a function of initial biomaterial processing [1,2].

Methods & Materials

Disks of CPP were prepared using a gelling/compaction method developed by Dion *et al* (termed "G1" disks) [2], with a second batch of disks produced using a secondary re-gelling/compaction step developed by Petrone *et al* (termed "G2" disks) [3]. All disks were made with a final (dry) diameter of 4 mm and thickness of 2 mm. The use of the G2 process has been shown, using conventional bulk elution protocols, to significantly extend the period of vancomycin release.

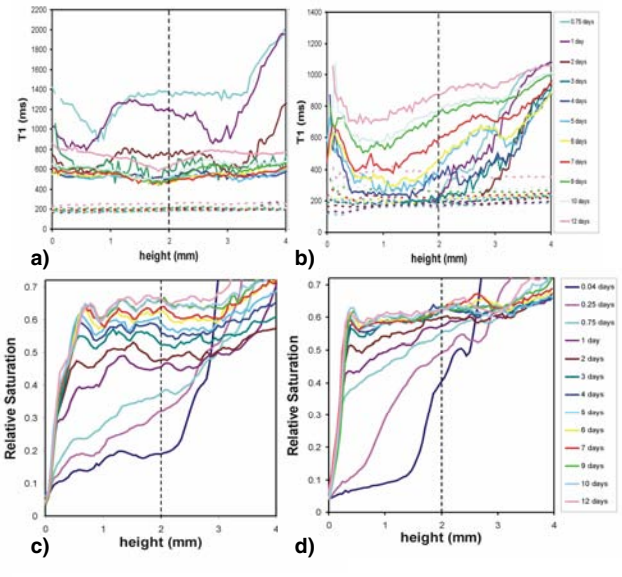

Figure 1. T_1 maps of a) G1 and b) G2 disks, and Fluid density maps of c) G1 and d) G2 disks, over 12 days of immersion in PBS. X-axis is height along the disk. Vertical dashed line shows the original height of the disk.

All MR data were acquired using a Bruker 11.7-T vertical bore system. CPP disks were fixed into standard 5-mm i.d. NMR tubes, resulting in a purely 1D flow of PBS solution that was introduced on top of the disk. Maps of fluid density were obtained using a spin-echo imaging sequence (TR/TE = 10000/1.48 ms, NEX = 32) with a spatial resolution of 49 µm. By including an inversion pulse, that same sequence was used to obtain maps of spin-lattice relaxation time, T_1, with identical spatial resolution (32 inversion times, NEX = 8). Maps of density and T_1 were collected at time points ranging from 1 hour to 12 days after immersion in PBS solution.

Results & Discussion

Figure 1 shows the time series of 1D maps of T_1 and fluid density, plotted as a function of height. With the exception of the early time points for G2 disks (<3 days), all T_1 data were best fit to a bi-exponential model. The maps indicate several features of both fluid transport into the material and the resulting network reorganization that takes place due to material degradation.

Differences in the rates of fluid ingress, saturation level, and T_1 values (and their relative amplitudes) are readily apparent between CPP disks produced using the G1 versus G2 method. In particular, it is interesting to note that during the period of fluid transport (< 7 days for G1, < 3 days for G2) the T_1 values and amplitudes are relatively static, with the only exception being a decrease in the long T_1 value for G1 disks. However, as shown in Fig. 2 (results extracted from a single pixel in the middle of the disk), immediately following the period of fluid transport the values and relative amplitudes for the T_1 maps begin to change. This likely indicates an internal reorganization of the CPP polymer network that is not linked to a change in density.

Conclusions

MR microscopy and relaxometry were successfully used to study differences in fluid transport and network reorganization in CPP disks that are due to initial material processing. Further studies are on-going to more fully characterize biomaterial degradation (e.g. ADC mapping), as well as to provide direct mapping of drug transport in CPP materials containing the drug vancomycin. Improved understanding of CPP degradation and drug release characteristics will lead to the improved development of drug delivery devices.

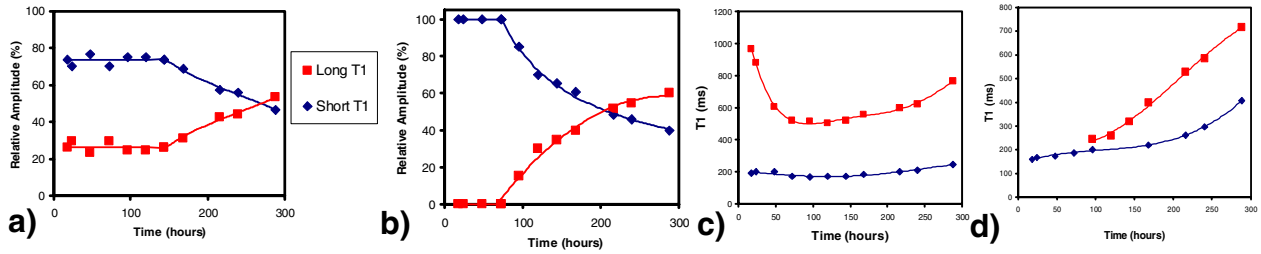

Figure 2. Bi-exponential data extracted from the T_1 maps (data for a single pixel, located in the middle of the material). Plots of relative amplitude vs. immersion time are shown in a) G1 and b) G2 disks. Plots of T_1 vs. immersion time are shown for c) G1 and d) G2 disks.

References

[1] Bray *et al*, "Measurement of Fluid Ingress into CPP Bioceramics using NMR Microscopy" *J. Magn. Reson.* (submitted) . [2] Beyea *et al*, "NMR Imaging of Functionalized Bioceramics" in NMR Imaging in Chemical Engineering Wiley-VCH, Weinheim Germany, S. Stapf and S. Han Editors, (2006). [3] A. Dion *et al*, "The effect of processing on the structural characteristics of Vancomycin-loaded amorphous calcium polyphosphate matrices" *Biomaterials*, 26, 4486-4494 (2005). [4] C. Petrone, Degradable calcium polyphosphate compaction strategies for the delivery of therapeutic agents, Master's thesis, Dalhousie University (2005).