Quantitative Ocular Pharmacokinetics Study in Rabbit using T1 Mapping

X. Shi[1], X. Liu[2], X. Wu[3], Z. Lu[4], K. Li[5], and E. Jeong[6]

[1]Department of Physics, University of utah, Salt Lake City, Utah, United States, [2]Department of physics, University of Utah, Salt Lake City, Utah, United States, [3]Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, Utah, United States, [4]Department of Pharmaceutics and Pharmaceutical Chemistry, university of utah, Salt Lake City, Utah, United States, [5]Division of Pharmaceutical Sciences, University of Cincinnati, Salt Lake City, Utah, United States, [6]Department of Radiology, University of utah, Salt Lake City, Utah, United States

INTRODUCTION: Recent advances in drug discovery have led to the development of effective therapeutic agents for the treatment of posterior eye diseases. However, drug delivery to the posterior eye remains a challenge and intravitreal injection continues to be the most common method in ocular drug delivery to the back of the eye [1]. Improvements of eye disease treatment based on novel drug delivery methods depend on reliable pharmacokinetics data [2-3]. The investigation of ocular pharmacokinetics by traditional methods is invasive and inconvenient. Recent studies have demonstrated the feasibility of using MRI to study the distribution and clearance of contrast agents in the eye in ocular pharmacokinetics study and ocular delivery method testing. Biodegradable polymers can be used in targeted drug delivery in the eye and as a drug delivery matrix for sustained ocular delivery. The use of MRI to study the distribution of biodegradable synthetic polymer in the eye would help us understand the ocular drug-delivery mechanism and clearance after intravitreal injection [4]. Because it is not possible to directly image the drug molecule using the conventional MR imaging due to the extremely low quantity of the NMR nuclei, paramagnetic ion-based contrast agent is generally used to indirectly measure the biodistribution of the compound. In this report, we present an MRI study of polymerized biodegradable drug surrogate conjugated with Gd-chelate that was injected into the rabbit eye. For the accurate quantification of the drug concentration, ΔR_1 ($=\frac{1}{T_1(C)}-\frac{1}{T_1(0)}$) was measured using 3D multishot double spin echo-planar imaging with automated variation of TR and TE (ms-DSEPI-T12) [5], which is known to be directly proportional to the concentration of the Gd-based contrast agent (GBCA), unlike MRI signal intensity of which is not linear to the local concentration of the paramagnetic ion.

METHODS: 100 μL, 1.3 μmol-Gd/ml of (Gd-DTPA)-Cystine Copolymers (GDCP) with molecular weights 21 k and 144 k Dalton was injected into the vitreous humor of rabbit eyes. The same dose of MultiHance™ (Bracco Diagnostics, Inc.) was injected into the different eyes as the control. Imaging studies were performed on a 3 T clinical MRI system (Trio-Tim, Siemens Medical Solutions, Erlangen, Germany) with Avanto gradients (45 mT/m strength and 150 T/m/s slew rate) using a manufacture's wrist coil. T_1 weighted spin-echo imaging was conducted before and 12 min, 2.5 hour, 4.5 hour, 8.5 hour, 12 hour, 1 day, 2 day, 1 week, 2 week and 1 month after injection of GBCAs and T_1 map imaging using 2D ms-DSEPI-T12 was implemented before and 3 min, 2.25 hour, 4.32 hour, 8.5 hour, 12 hour, 23.8 hour, 2 day, 1 week, 2 week, 2 week and 1 month after injection of GBCA. Imaging parameters for spin-echo imaging were TR/TE=602/11 ms, 128x80 acquisition matrix, 10 slices, 1.0x1.0x1.0mm^3 spatial resolution. And imaging parameters for T_1 mapping using 2D ms-DSEPI-T12 were 12 slice, 128x40 acquisition matrix, 1.0x1.0x2.0 mm^3 resolution, 1086 Hz/Pixel bandwidth, ETL 7, and TRs/TEs of 138/32, 338/42, 738/52, 1528/62, 2318/72 and 3108/82 ms. The change $\Delta R_1(t)$ of the relaxation rate was summed over the each eye by manual segmentation.

RESULTS & DISCUSSION Figs.1a and 1b show the T_1-weighted 2D spin-echo images of rabbit eyes before and at various time points after injection with the different contrast agents. The low molecular weight conjugate MultiHance™ was cleared from the eye in the first 12 h post-injection. GDCP conjugates with the high molecular weight (144 and 21 kDa) had much longer eye retention time, which lasted 2 days. Figs.1c and 1d show the T_1 map of the results in Figs. 1a and 1b. The dynamic changes of T_1 relaxation time represent the conjugate pharmacokinetics after injection, and the sharp decrease in T_1 values in the rabbit eye corresponds to an increase of conjugate concentration. Since the concentration of gadolinium has a linear correlation with ΔR_1, the normalized sum of $\Delta R_1(t)$ was plotted in Fig. 2 for three GBCA data sets. Figs.2a and 2b show fast change of ΔR_1 during the first 100 minutes after injection of MultiHance™ . Because the diffusive rate of molecules in vitrous humors depends on the molecular weight of GBCA, MultiHance™ with smaller molecular weight was cleared faster compared with GDCP (Fig.2a, b). Interestingly, macromolcular GDCP 144 k and 21 k showed the same clearance patterns (Fig. 2c) independent on their molecular weight, suggesting that the 144 k biodegradable polymer might have broken into smaller fragments in the vitreous humor over time.

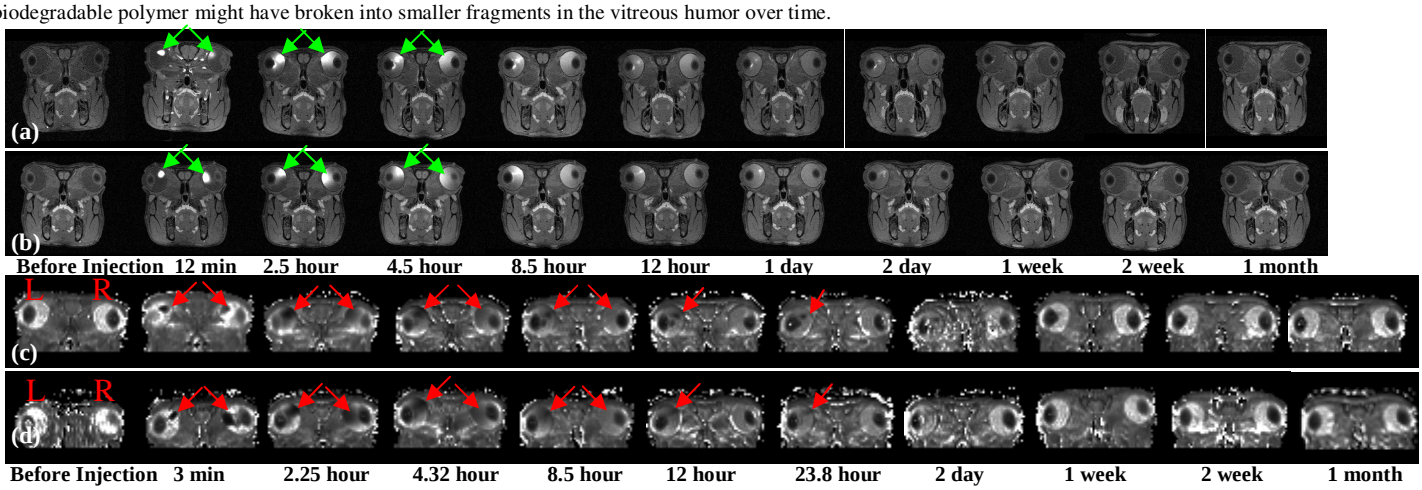

Figure 1: Signal changes with (a) GDCP (144 kDa, left eye) and MultiHance (right eye) in Rabbit 1. (b) GDCP (21 kDa, left eye) and MultiHance (right eye) in Rabbit 2. (c, d) T_1 maps computed using MR images obtained by ms-DSEPI-T12 for (c) GDCP (144 kDa, left eye) and MultiHance (right eye), (d) GDCP (21 kDa, left eye) and MultiHance (right eye).

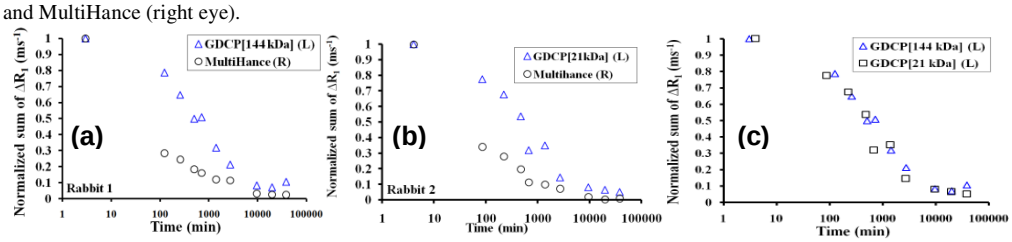

Figure 2: Normalized summation of ΔR_1 of the whole vitreous humor of Rabbit 1 and Rabbit 2. (a) ΔR_1 in left (L) and right (R) eye of rabbit 1. (b) ΔR_1 in left (L) and right (R) eye for rabbit 2. (c) ΔR_1 in left eyes of Rabbit 1 and Rabbit 2 with GDCP 144 k and 21 k Da injection.

ACKNOWLEDGEMENTS: This work was supported by NIH grant EY 015181.

REFERENCE: [1] Ghate D et al. Expert Opin. Drug Deliv. 2006; 3: 275-287. [2] Rudin M et al. Nat. Rev. Drug Discov. 2003;2: 123-131. [3] Mader K et al. J. Pharm. Sci. 1997; 86: 126-134. [4] S. Kevin Li et al. NMR Biomed. 2007; 20:1-6. [5] Xin Liu et al. ISMRM. 2007; p5617, Berlin, Germany.