Temporally-Controlled Shape Memory Polymers for Drug Delivery

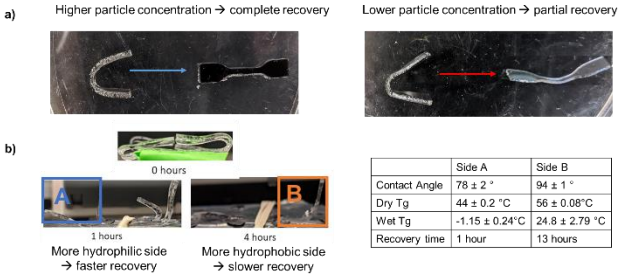
Anand Utpal Vakil, Yohely Espiritusanto, Dr. Era Jain and Dr. Mary Beth Browning Monroe
Biomedical and Chemical Engineering, BioInspired Syracuse, Syracuse University, Syracuse, New York

Statement of Purpose: Over 90% of hospitalized patients receive some form of infusion therapy, in which drugs are delivered intravenously.[1] These treatments have several limitations, including uneven drug distribution and the inability of drugs to reach target sites at required doses.[2] Current research to address these issues focuses on using drug-loaded polymers that can be implanted at the target site. Thermally-induced shape memory polymer (SMP) elastomers have the capability to deliver drugs via passive burst release that can last over 700 hours, but cannot be activated remotely.[3] Magnetic hydrogel nanocomposites have the capability to deliver drugs on-demand via external stimulus (i.e. magnetic field) to deliver drugs, but can only be used for a maximum of 7 hours.[4] Both approaches are limited to a single release.

To improve upon these systems, we propose to use magnetically-responsive SMPs with temporally-controlled delivery combined with variations in polymer chemistry to tune shape recovery rates.[5], [6] These polymers are synthesized with uniform drug concentration and varied magnetic particle concentrations and strained into a fixed, secondary shape that limits drug diffusion. Upon application of an alternating magnetic field at a fixed frequency, the magnetic particles are excited, which triggers shape recovery and subsequent drug release. By varying magnetic particle concentration within a single implant, we can control drug release over multiple remote triggers.[7] Here, we present a proof-of-concept for the proposed magnetically responsive SMPs.

Methods: *Microparticle synthesis:* Fluorescently-labelled PEG-PLGA microparticles loaded with acridine orange were synthesized using a microfluidics system as previously described.[8] *Magnetic nanoparticle synthesis:* Magnetic particles (Fe_3O_4) were prepared via wet chemical reduction as described by Chaki et al.[9] Sodium borohydride (2.5M) was used to reduce ferric chloride hexahydrate (0.1M) in a 1:4 volume ratio aqueous solution to form Fe3O4 using a wet chemical reduction method.[8] Vigorous mixing was maintained during dropwise addition of ferric chloride to sodium borohydride, and resulting Fe3O4 precipitates were washed with DI water and methanol before drying overnight at 50°C. Magnetic particle hydrodynamic diameter was measured using a Zeta analyzer. *SMP synthesis:* Shape memory polyurethane films were synthesized by mixing varying combinations of hydroxyls and isocyanates to tune crosslink density and hydrophilicity. Hydroxyl components consisted of N, N,N',N'-tetrakis-2 hydroxypropyl ethylenediamine (HPED), triethanolamine (TEA), and trimethylolpropane (TMPAE). Isocyanates consisted of hexamethylene diisocyante (HDI) and 2,2,4-trimethyl hexamethylene diisocyante (TMHDI). To increase crosslink density, polymers were UV crosslinked using di and tetrafunctional crosslinkers via thiolene click chemistry.[10] Fluorescent microparticles and/or magnetic nanoparticles were mixed into the system at varying concentrations prior to crosslinking. *Characterization:* Glass transition temperatures (Tg's) were quantified using differential scanning calorimetry. Dye release before and after shape recovery was characterized using spectroscopic measurements. Shape memory properties in response to heat and a magnetic field were characterized to determine effects of nanoparticle contents on recovery rates.

Results: Films were loaded with varying concentrations of magnetic particles to compare differences in actuation time. Higher nanoparticle concentrations provided complete shape recovery under a magnetic field, while lower concentrations resulted in partial recovery **Figure 1a**. In a separate study, films were synthesized with a gradient of hydrophobicity and subjected to volume recovery experiments in water. The more hydrophilic side recovered faster than the hydrophobic side, providing a potential mechanism for varying release rates within a single scaffold.



	Side A	Side B
Contact Angle	78 ± 2 °	94 ± 1 °
Dry Tg	44 ± 0.2 °C	56 ± 0.08°C
Wet Tg	-1.15 ± 0.24°C	24.8 ± 2.79 °C
Recovery time	1 hour	13 hours

Figure 1. Foam characterization: a) volume recovery under magnetic field, b) variation in volume recovery times in 37°C water based on hydrophobicity and glass transition temperature.

Conclusions: Thus far, we have developed two mechanisms for tuning shape recovery rates: Fe_3O_4 particle concentrations under magnetic field and hydrophobicity. These mechanisms could be used together to provide remotely-triggered drug delivery with precise time frames for SMP recovery and subsequent drug release. Current work focuses on loading films with drug-loaded microparticles to characterize drug release during shape recovery under a magnetic field and/or in body temperature water. In the long-term, this system could be used to sequentially deliver different drugs from the same scaffold at controlled time frames.

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