Flexible control over the rate and timing of drug delivery from magnetically responsive hydrogels

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Statement of Purpose: Magnetically responsive hydrogels are promising biomaterials in applications that require remotely activated, on-demand drug delivery. While these biomaterials have been shown to deliver drugs, growth factors, plasmid DNA, and adherent cells when magnetically stimulated, explicit control over delivery rates and long-term drug retention prior to stimulated release has yet to be demonstrated. These additional capabilities are particularly important in regenerative engineering, where flexible control over the dose and timing of growth factor delivery is desirable in order to coordinate a sequence of recruitment, proliferation and differentiation events. We hypothesized that improved strategies for regulating the rate and timing of drug delivery required a better understanding of (i) how the frequency of magnetic stimulation and (ii) how the interactions between the drug and hydrogel's polymeric matrix, each, influenced retention and release dynamics from magnetically responsive gels.

Methods: Magnetically responsive ferrogels containing 1% wt alginate, 5 mM adipic acid dihydrazide, and 7% wt iron oxide were freeze-dried at -20°C to produce macroporous and magnetically deformable gels (Fig. 1A, top). After lyophilization, ferrogels were loaded with mitoxantrone, detxtran, or BMP-2. On a custom electromagnet system (Fig 1A, bottom), we were able to expose drug-laden ferrogels to magnetic frequencies ranging from 1-550 Hz. Mitoxantrone release was measured via optical absorbance at 610 nm, FITC-labeled dextran release was measured via fluorescence excitation/emission at 495/519 nm, and BMP-2 release was quantified using ELISA. 30 minutes of magnetic stimulation per day at 1Hz was used in dextran release studies and 8 hours of continuous 1 Hz magnetic stimulation was used in BMP-2 release studies. Plotted data represents means and standard deviations (N = 4).

Results: Ferrogels released mitoxantrone at frequency-prescribed rates with an optimal release rate centered at 20 Hz (Fig. 1B). While the rate of drug delivery could be explicitly regulated by varying the frequency of magnetic stimulation either below or above 20 Hz, in the rage of 20 Hz to 500 Hz, ferrogels released drug without noticeably deforming. This is notably advantageous in regenerative applications that demand immobilized cell scaffolding (e.g., bone regeneration).

Analysis of how the size and net charge of model drugs influenced retention and magnetic release dynamics (Fig. 1C) employed a low affinity 4 kDa dextran with one negative charge due to FITC labeling (red curves), a moderate affinity 4 kDa dextran with a +3 net charge due to DEAE substitution (blue curves), and a high affinity 150 kDa dextran with a +120 net charge (green curves). For prolonged retention, high affinity was required (Fig. 1C, green curves compared to red and blue curves). However, because of this high affinity, magnetic stimulation was not able to liberate dextran from the gels (Fig. 1C, green dashed curve) compared to controls (green solid curve). Magnetic stimulation was also ineffective for engendering the release of moderate and low affinity dextran (Fig. 1C, comparing solid and dashed blue and red curves). This was likely due to insufficient magnetic stimulation and amount of remaining dextran on day 5.

In order to magnetically trigger release after prolonged periods of retention, a drug with high affinity for alginate was used (i.e., BMP-2) and a new ferrogel design was implemented that allowed for enhanced magnetic deformation. This was achieved by physically partitioning our ferrogels into a magneto-mutable region (Fig. 1D, SEM inset, pink colored region) and a deformable, drug-harboring region (purple colored region). This biphasic design allowed for excellent BMP-2 retention for 5 days (< 10 ng/min) and efficient release when stimulated on day 5 (300-400 ng/min) (Fig. 1D, graph).

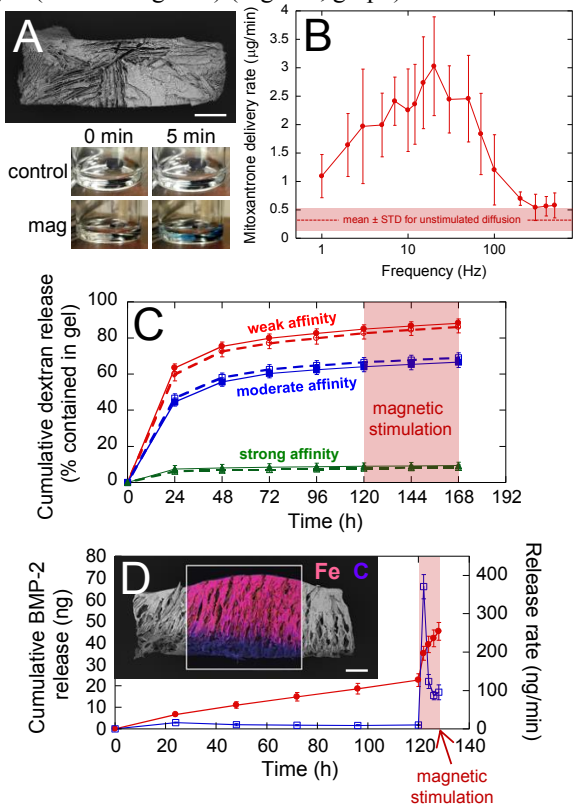

Figure 1. (A) SEM micrograph of ferrogels (top) and images from release experiments (bottom). (B) Release rate vs. frequency. (C) Release from stimulated gels (dashed) and control gels (solid) for weak, moderate and strong affinity dextran. (D) Biophasic ferrogel SEM (inset) and BMP-2 retention and release over 6 days.

Conclusions: Magnetically responsive ferrogels released drug at frequency-controlled rates and could be designed to provide excellent growth factor retention and release profiles. We believe these studies demonstrate how these hydrogels can be powerful tools in regenerative engineering, providing great flexibility in coordinating the dose and timing of growth factor delivery.