Metal Implants and Immune Response: Characterization of Burst Nickel Release from Nitinol

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Introduction

- Nitinol is composed of ~50% Ni and Ti. Ni release is a toxicological concern.
- Ni release is conventionally evaluated with long term (> 2 months) soaking in physiological conditions per ASTM F3306-19.
- Accelerated testing by soaking at higher temperatures has been proposed [1]; this study aims to elucidate the mechanisms for extrapolating Ni release.
- A Ni release model including terms for burst and sustained release [2] is evaluated and a method for rapid sampling is proposed to better investigate burst release.

The **purpose** of this work is the development of tools that shorten the duration of benchtop testing while providing reliable results.

Research Question

Is the proposed model (Equation 1) appropriate for Ni release during the burst (< 1 day) release phase?

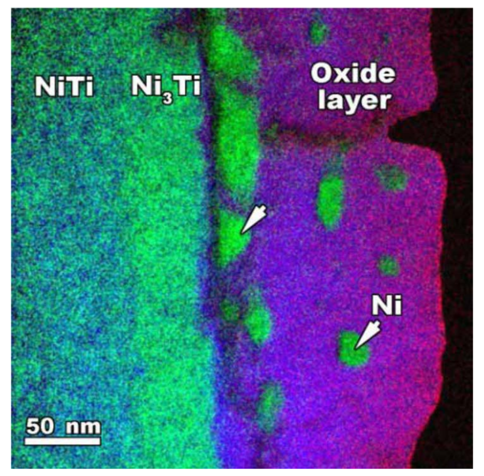

Figure 1. Representative EFTEM image of a nitinol oxide layer from reference [3]. Note the Ni-rich phases near the surface, which contribute to burst release.

Equation 1. Ni release rate ($\dot{M}_d$) per unit area can be modeled as the sum of burst and sustained (Higuchi) release [2].

$$\frac{\dot{M}_d(t)}{A} = \underbrace{\frac{8\alpha e^{-t/\tau}}{\pi^2 \tau}}_{\text{Burst Release}} + \underbrace{\frac{ß}{2\sqrt{t}}}_{\text{Sustained Release}}$$

- α – Burst phase Ni mass per unit area
- τ – Characteristic release time of burst phase
- ß – Sustained release rate per unit area

Materials and Methods

Nitinol Test Article
- Meets ASTM F2063-12 specification
- Dimensions: 50.8 x 57.2 x 0.5 mm plate
- Superelastic (A_f temperature = -5^{o}C ± 5^{o}C)
- Cold rolled (R_a = 0.24μm)

Sample Extraction and Sampling
- Per ASTM F3306-19
- Test solution: Phosphate-buffered saline
- Extraction Ratio: 6 cm^2/mL
- Sampling: 15 min or 1 hr over 6 hr

Trace Metal Analysis
- Inductively Coupled Plasma Mass Spectrometry (ICP-MS)
- Samples diluted 5x to 2 vol% nitric acid
- Kinetic energy discrimination (KED mode) used for analysis

Model Fitting
- Fit generated from N=4 independent replicates
- Inverse weighting by standard deviations
- Activation energies of burst and sustained release calculated assuming Arrhenius kinetics.

Results – A first look at short-term Ni Release

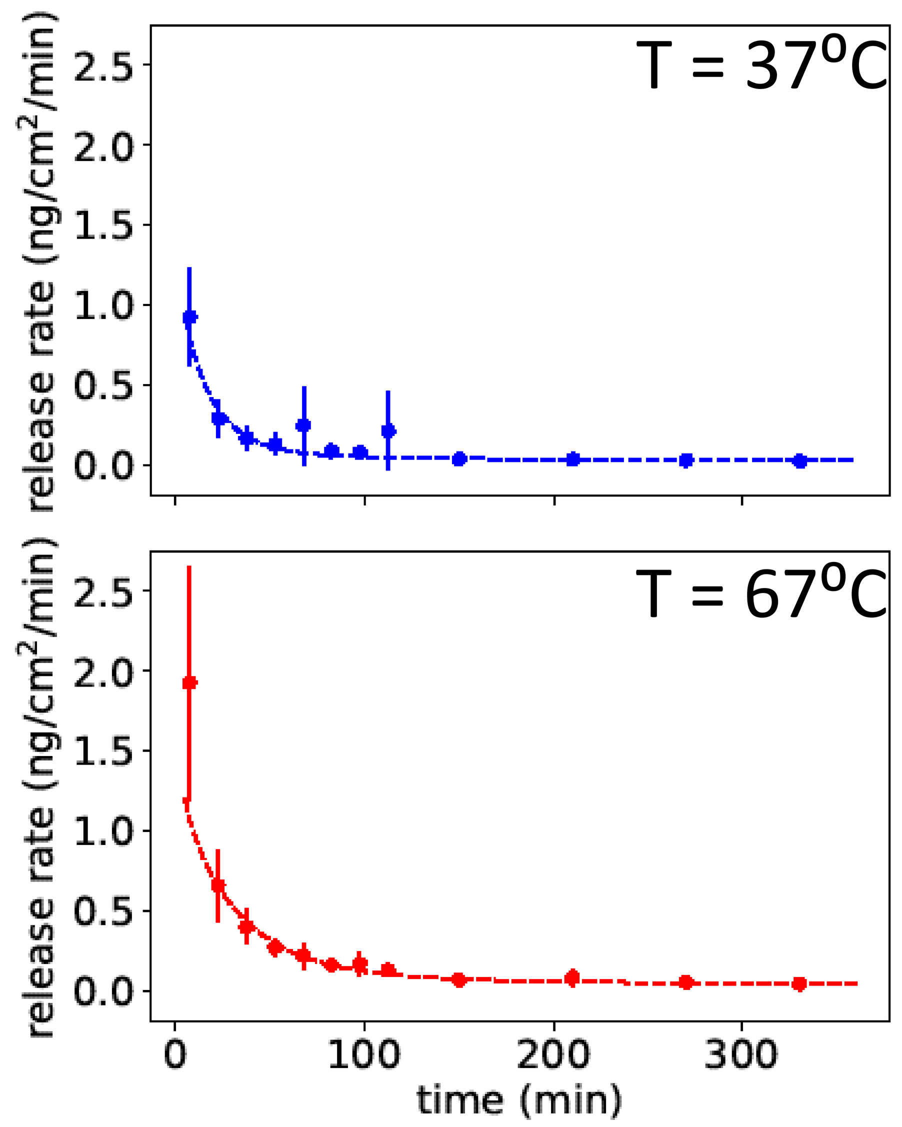

Figure 2. (left top) Ni release rates for 37 °C and (left bottom) 67 °C. Values represent means and standard deviation of N=4 independent replicates. Dashed lines represent the model fit.

Model Fit Parameters

Temperature (K)	α (ng/cm²)	τ (min)	β (ng/min$^{1/2}$/cm²)
310	19.87 ± 3.36	16.55 ± 3.62	0.92 ± 0.11
340	39.25 ± 5.49	31.59 ± 4.81	1.52 ± 0.13
E_a (kJ/mol)		-18.90	29.32

Table 1. Tabulated fit parameters to Equation 1 and activation energies of the two mechanisms calculated from Equation 2.

$$E_a = \frac{R \ln \frac{k_{67°C}}{k_{37°C}}}{\frac{1}{310.15K} - \frac{1}{340.15K}} \qquad k_{Burst} = {}^{1}/_{\tau} \qquad k_{Sustained} = ß^2$$

Equation 2. Arrhenius equation solved for activation energy given reaction rates at two temperatures.

Discussion

- This preliminary data shows increasing T increases α contrary to assumptions; more Ni is available during the burst phase. **This causes τ to increase which falsely results in a negative activation energy.**
- Sample-to-sample variability and handling difficulties due to short time intervals should be addressed with a more sophisticated apparatus (see below).

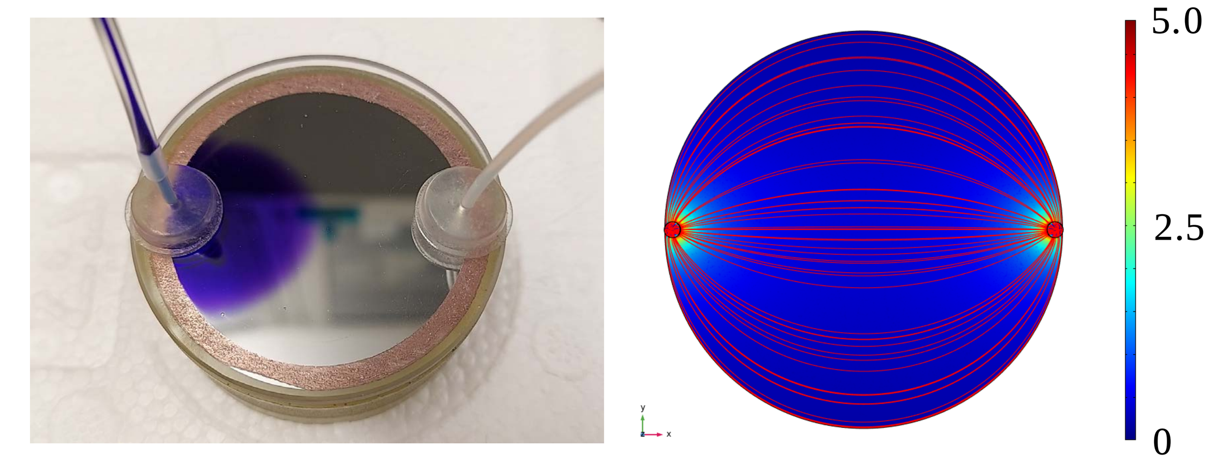

Figure 5. (left) Flow cell prototype containing Crystal Violet dye for flow visualization. Dye is cleared from the flow cell in approximately 4 minutes at a 100 μL/min flow rate. (right) COMSOL flow simulation for a 60 μL/min flow rate in a circular flow cell. Color gradient represents fluid velocity. Red lines represent streamlines.

Proposed Apparatus

Goal: Decrease sample variability and increase time resolution

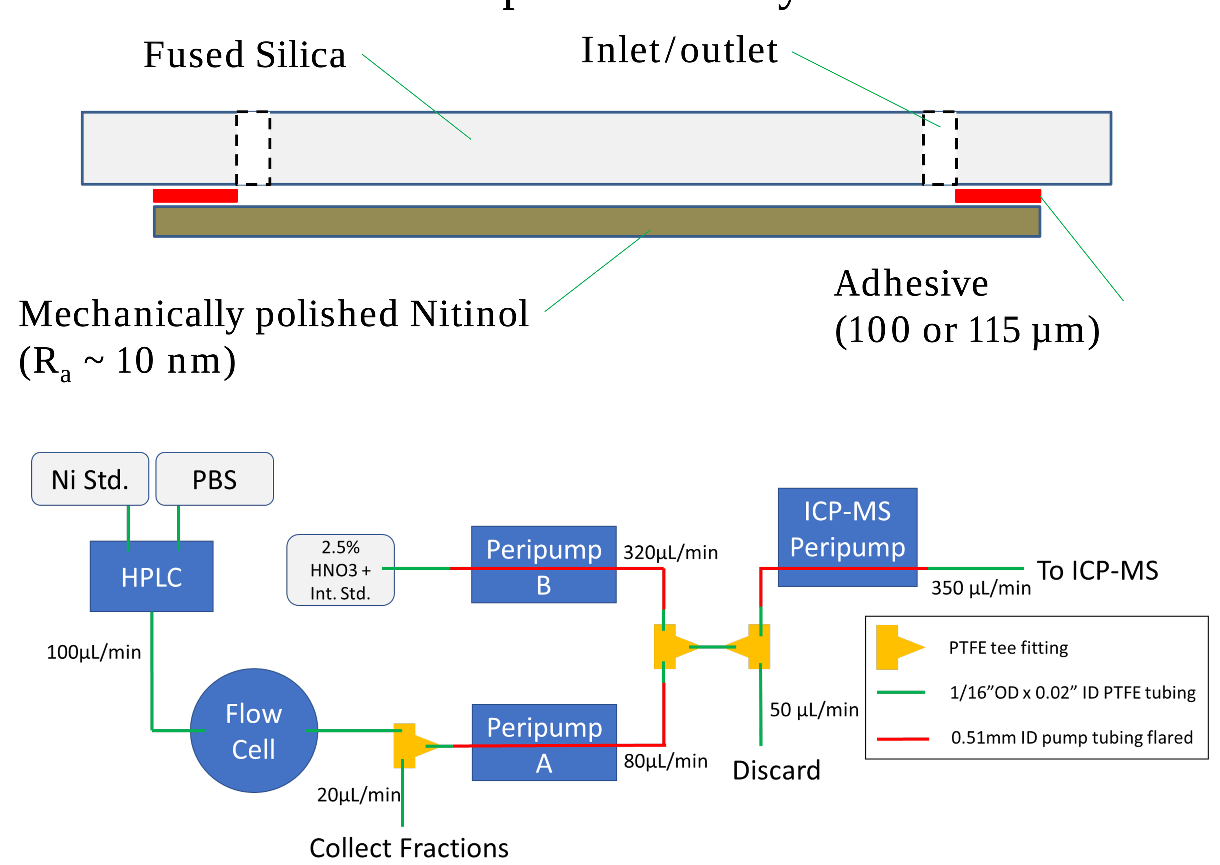

Figure 3. (top) Side-view diagram of adhesive-based microfluidic flow cell. Nitinol surface finish is tightly controlled. (bottom) Proposed fluidics setup to feed acidified samples to the ICP-MS while simultaneously collecting fractions for conventional trace metal analysis.

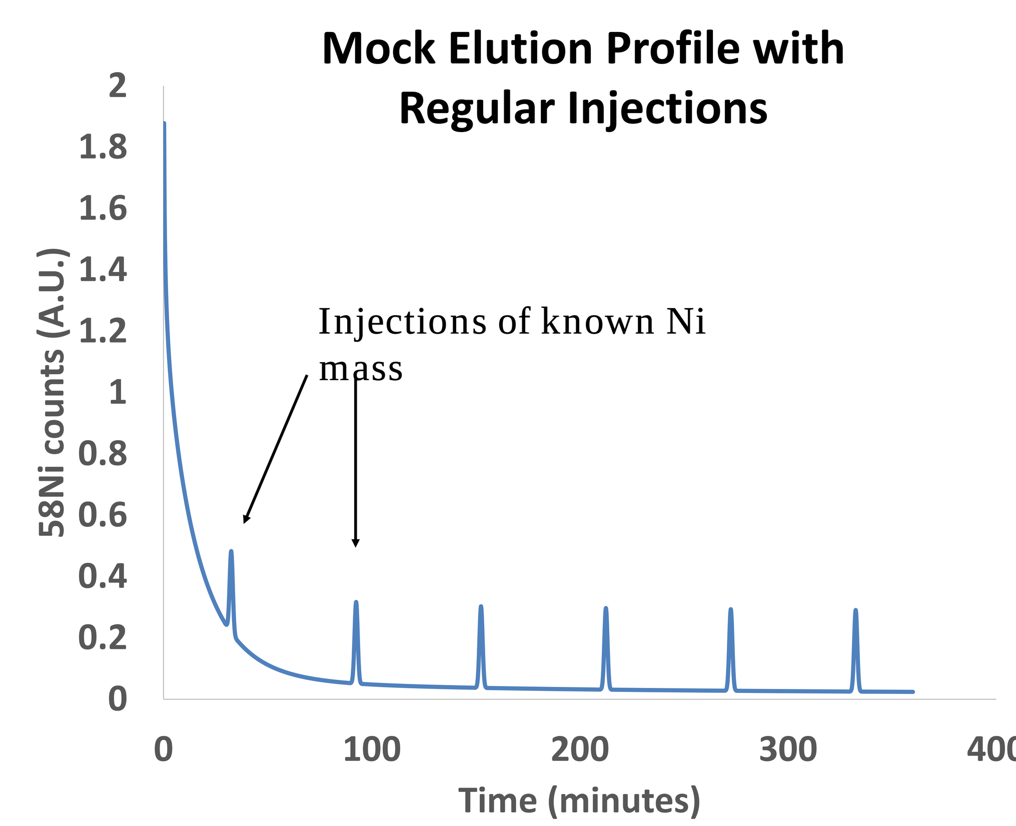

Figure 4. Mock data of continuous Ni measurements with regular injections of known Ni mass. Injections can be used to correlate area under the curve to Ni mass. Calculations can be verified with conventional ICP-MS of fractions collected during the experiment.

Preliminary Conclusions

- Early (6 hr) Ni release follows bi-phasic profile; diffusion is the rate limiting mechanism.
- Apparent temperature dependence of **α** violates an assumption of the model; additional considerations (e.g., chemical reactions) could be added to the model.

Challenges and potential solutions

- High sample-sample variability in burst phase limits confidence
  - Perform test using better controlled surface finish by mechanically and/or electropolishing
  - Develop apparatus to continuously monitor Ni release automatically to reduce experimenter error.

Future Work

- Validate Arrhenius behavior by testing at additional temperatures
- Investigate temperature dependence of α
- Investigate different method and material parameters to better replicate *in vivo* corrosion and predict varying Ni release due to different manufacturing methods.

Ultimate objective: Develop a tool for predicting worst case daily Ni exposure to reduce the burden of regulatory submission.

References

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