# Ultrasound-Enhanced Drug Delivery for Treatment of Onychomycosis

**Alina Kline-Schoder[1], Zung Le[2], and Vesna Zderic[1]**

[1]Department of Biomedical Engineering, The George Washington University

[2]Podiatry, Medical Faculty Associates, The George Washington University

## PURPOSE

Onychomycosis is a fungal nail infection that is characterized by thickened, discolored nails with subungual debris that can be extremely painful and lead to psychosocial issues. In onychomycosis, the fungus lives in the nail bed. Due to the poor permeability of the nail, current antifungal drugs, which are applied to the top of the nail, are unable to reliably reach the nail bed, making them ineffective in treating the fungus. The objective of this study is to use low intensity ultrasound to promote the permeability of the nail.

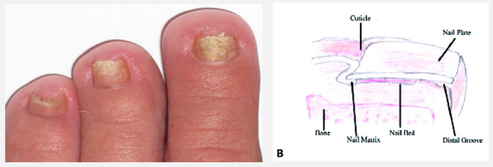


**Fig. 1:** Toenail with onychomycosis and nail cross section

## DISSATISFACTION WITH CURRENT TREATMENT

- As of 2007, 32 million Americans have onychomycosis.
- Around a quarter of diabetes patients have onychomycosis.
- Diabetics with onychomycosis have a greater risk of cellulitis, ulceration and gangrene.
- The best oral drug has to be taken for over 6 months, has a failure rate greater than 30%, and is associated with dangerous side effects, such as elevated liver function tests and hepatitis.
- The other treatment is a nail-polish drug that has only non-serious, infrequently reported side effects, but its cure rate is only 36% after 6 months of daily application.

## SPECIFIC AIMS

- Determine effectiveness of increased permeability of nail due to ultrasonic application.
  - ➢Performed luminosity color measurements.
  - ➢Performed diffusion cell measurements.
- Determine safety of ultrasound application.
  - ➢Modeling studies of temperature increase in human toe exposed to ultrasound were performed

## PZFLEX

- PZFlex is an analysis software, that utilizes a finite-element approach and an explicit time-domain.
- It was used to calculate the exact ultrasound intensity in both the luminosity and diffusion cell experiments at all frequencies.
- It was also used to calculate temperature increase in the human toe due to ultrasound application at DFF.
  - ➢ Frequencies: 400 kHz, 600 kHz, 800 kHz, 1 MHz
  - ➢ Distance (DFF): 15.0 mm, 22.5 mm, 30.0 mm, 37.5 mm.

## GENERAL EXPERIMENTAL PARAMETERS

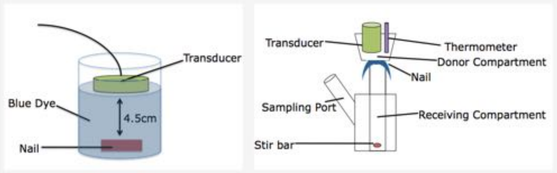


**Fig. 2:** Experimental setup for luminosity and diffusion cell experiments

- Pig feet were obtained from Siouxpreme Company, and the nails were separated using a scalpel and razor before being stored at 1.6˚C.
- Both setups were placed in a water bath at body temperature.
- Temperature was measured at all frequencies for each experiment.
- A planar ultrasound was used to sonicate the nails using a range of ultrasound parameters.
  - ➢Frequencies: 400 kHz, 600 kHz, 800 kHz, 1Mhz
  - ➢Intensity; 1 +/- .1 W/cm$^2$
  - ➢Duty Cycle: 100% (continuous) for a duration of 5 minutes

| Frequency | Luminosity Intensity (W/cm$^2$) | Diffusion Cell Intensity (W/cm$^2$) |
|---|---|---|
| 400 kHz | 1.02 | .99 |
| 600 kHz | 1.04 | .94 |
| 800 kHz | 1.06 | 1.03 |
| 1 MHz | .96 | .99 |

**Fig. 3:** Intensity of luminosity and diffusion cell experiments

## LUMINOSITY EXPERIMENT METHODS AND MATERIALS

- Pieces of porcine nail were placed in a 100 mL beaker, 35cm beneath the ultrasound transducer.
- The beaker filled with the blue dye which with a molecular weight of 792.84 g/mol, mimics the nail polish drugs used.
- Images were taken after treatment (**Fig. 4**).
- Cross section image was analyzed on Photoshop.
- Luminosity value (v) was developed using Photoshop brightness value (b).

V=10/b


**Fig. 4:** Sample pictures taken of nail exposed to the dye solution and ultrasound

## DIFFUSION CELL MATERIALS AND METHODS

- The donor compartment was filled with blue dye or Ciclopirox and the receiving compartment is filled with saline or ethanol.
- The nails were placed in an adaptor between the donor and receiving compartment.
- Ultrasound was applied 8.5 cm above the nail.
- After allotted time of application of ultrasound, the nail sat with dye or Ciclopirox to total 60 min exposure.
- After 60 min exposure, the permeability of the nail was measured by the absorption of the liquid in the donor compartment.

## RESULTS

- Our data indicated that application of low-intensity ultrasound can lead to increased permeability of the nail.
- A higher frequency corresponded to more permeation through the nail.
- Temperature increases as determined by PZFlex and thermocouples were found to be under 1.5˚C, and are expected to be safe in future applications in patients.

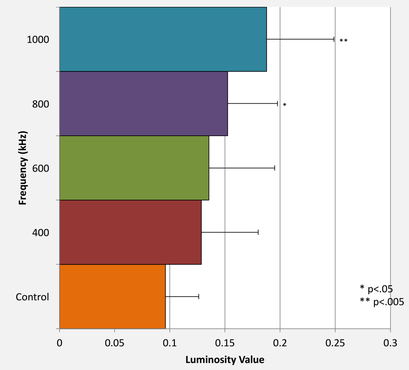


**Fig. 5:** Luminosity Results at Varying Ultrasonic Frequencies

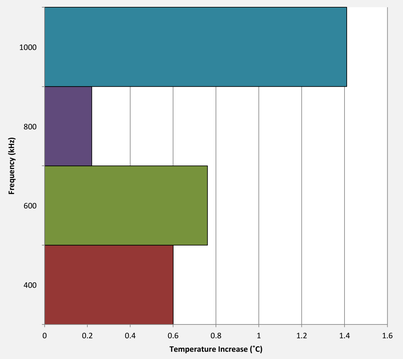


**Fig. 6:** Temperature Safety Modeling Maximum Increase

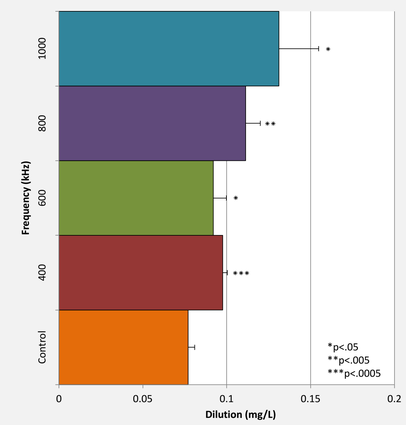


**Fig. 7:** Dye Dilution in Receiver Compartment

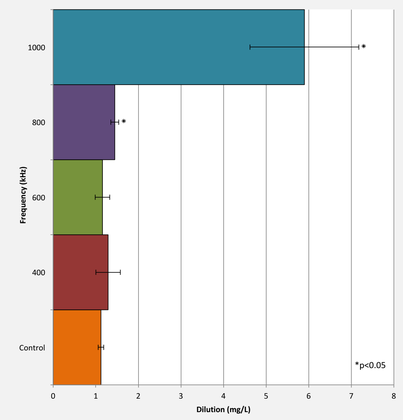


**Fig. 8:** Ciclopirox Dilution in Receiver Compartment

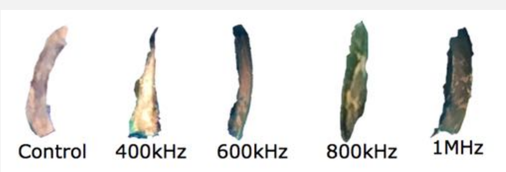


**Fig. 9:** Luminosity nail cross sections shown at various frequencies

## FUTURE STUDIES

- We plan to use mycotic human nails which are removed as part of normal treatment, in the diffusion cell setup.
- The parameters for ultrasound will be optimized within those deemed safe for humans.

## CONCLUSIONS

If proven successful our method may find a clinical application due to the non-invasive nature of therapeutic ultrasound treatment. Our results show a clear correlation between the application of ultrasound at increasing frequency and permeability of the nail. This suggests that our methodology may have a place in the clinical field and the ideal parameters may be found at a higher frequency. Additionally, the temperature measurements found using PZFlex suggest that this method is in fact safe for humans.

*Contact: alinaks@gwmail.gwu.edu