Microneedle enabled dual drug delivery system for vaginal infections using magnetic hyperthermia

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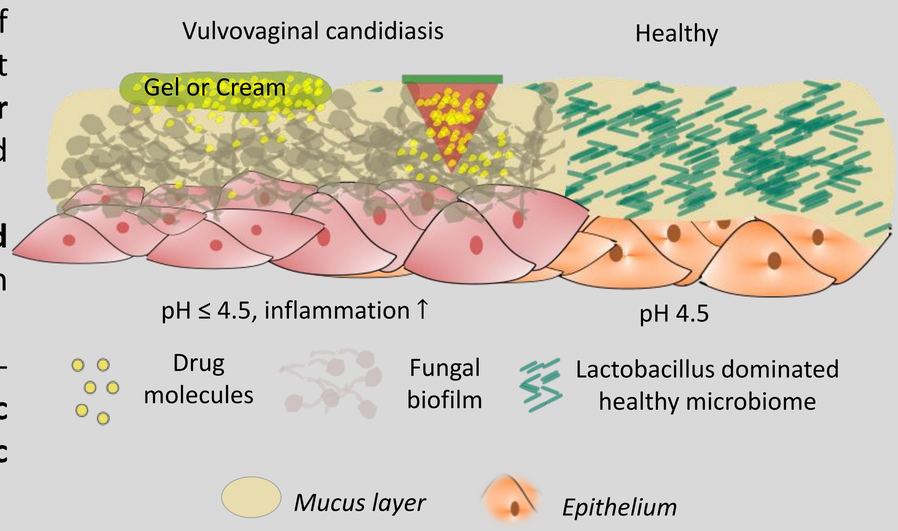
Introduction

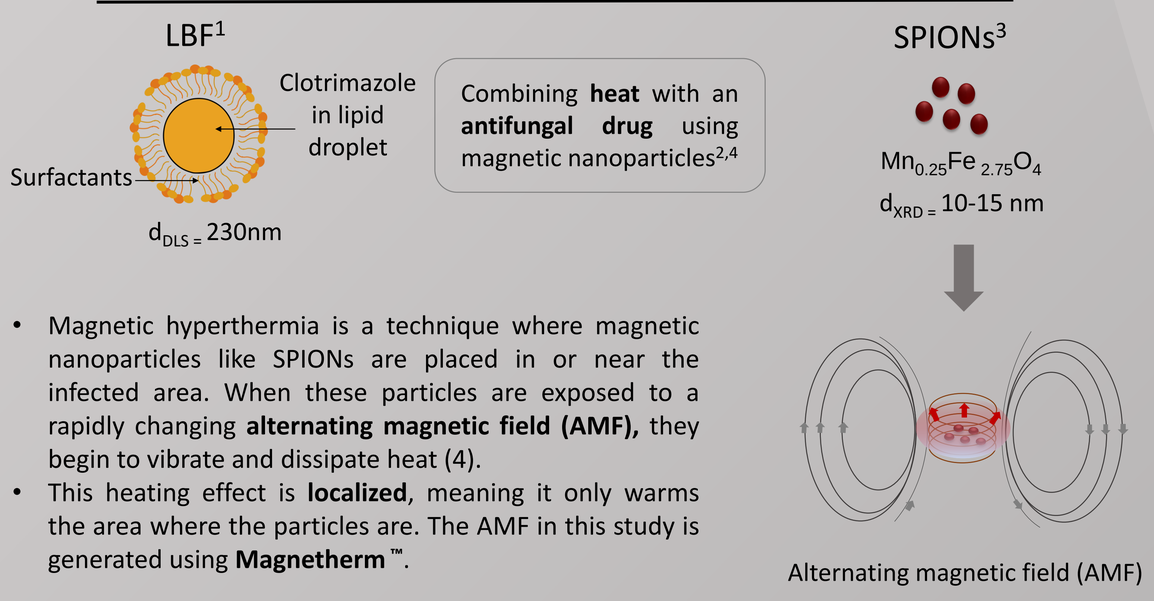
- **Vulvovaginal candidiasis (VVC)** affects ~75% of women, with majority experiencing recurrent infections. Current treatments struggle with **poor mucus penetration**, **limited drug retention**, and **rising resistance**.
- To overcome these barriers, **lipid-based nanocarrier** loaded with **clotrimazole** have been incorporated into **microneedles (1).**
- Here, we present a **dual-action strategy**: drug-loaded microneedles combined with **magnetic hyperthermia**, offering a potentially **synergistic approach** to disrupt *Candida albicans* biofilms (2).



Aim

- Utilizing microneedles, to develop a **dual drug delivery system** using anti-fungal clotrimazole and heat generated via **magnetic nanoparticles** like **Super Paramagnetic Iron Oxide Nanoparticles (SPIONs).**
- To fabricate **microneedles** with two types of nanoparticles: **SPIONs** and a **clotrimazole loaded lipid nanocarrier, lipid based formulation (LBF)**.
- Test **heating capacity** of the SPION loaded microneedles *in vitro* and *ex vivo*.
- **Explore a potentially synergistic antifungal effect** of heat and drug combination using suitable *in vitro* and *ex vivo* systems.

Nanoparticles for dual action

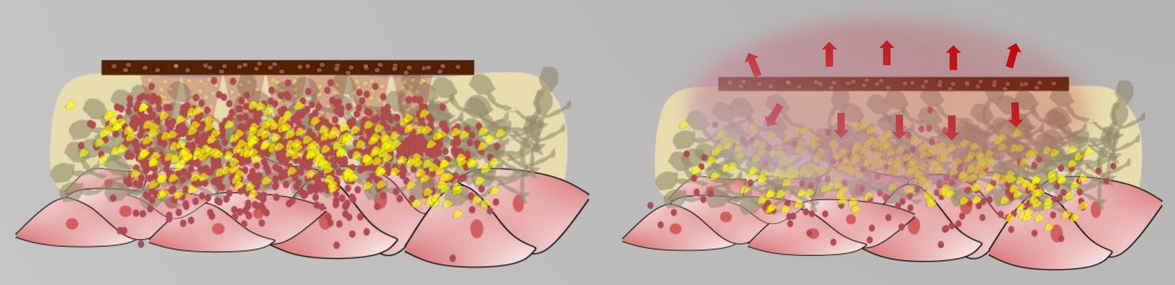


- Magnetic hyperthermia is a technique where magnetic nanoparticles like SPIONs are placed in or near the infected area. When these particles are exposed to a rapidly changing **alternating magnetic field (AMF),** they begin to vibrate and dissipate heat (4).
- This heating effect is **localized**, meaning it only warms the area where the particles are. The AMF in this study is generated using **Magnetherm™**.

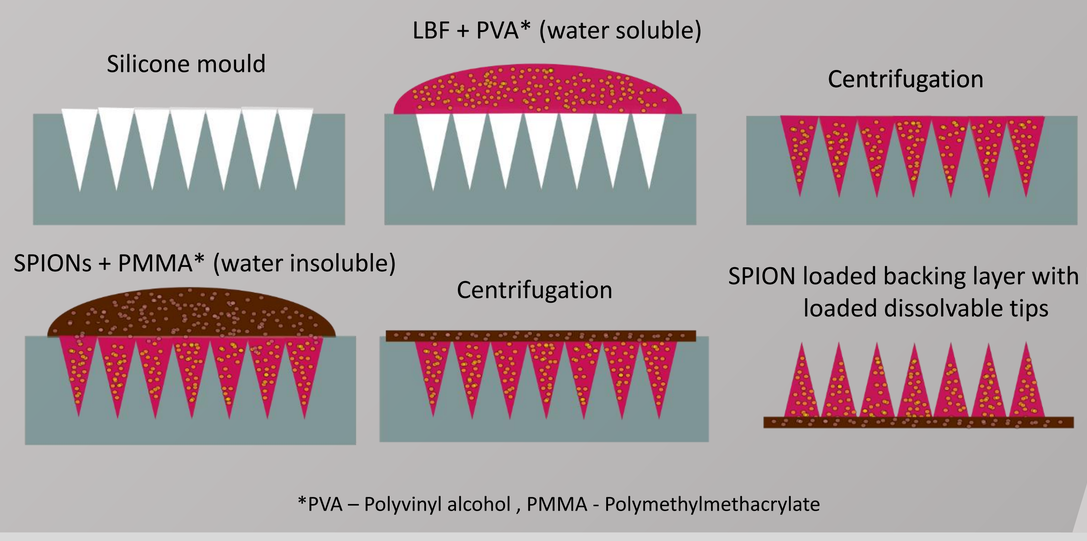
Dual drug delivery – a proof of concept study

- Microneedle tips containing **LBF in PVA**, dissolve and facilitate delivery of the nanoparticles past the mucus layer.
- The LBF will then have a **controlled release of clotrimazole** over time (1).

- **SPIONs incorporated in the non-dissolvable PMMA backing layer,** will later be used to **generate heat** at the target site when exposed to **AMF.**
- The **heating capacity of the patch** in air and when inserted on excised vaginal tissue will be tested using the Magnetherm™.



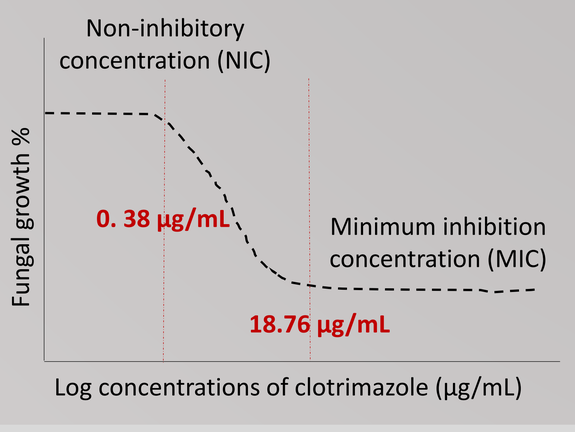
Nanoparticle loaded microneedles



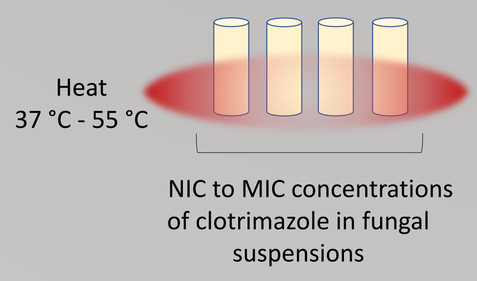
*PVA – Polyvinyl alcohol , PMMA - Polymethylmethacrylate

In vitro antifungal evaluation and synergy testing

In vitro growth curve analysis, to test fungal susceptibility against clotrimazole



Inhibition efficiency and synergy/additivity/antagonistic scoring will be estimated using *in vitro* fungal culture at different temperatures and clotrimazole concentrations between MIC and NIC



Results

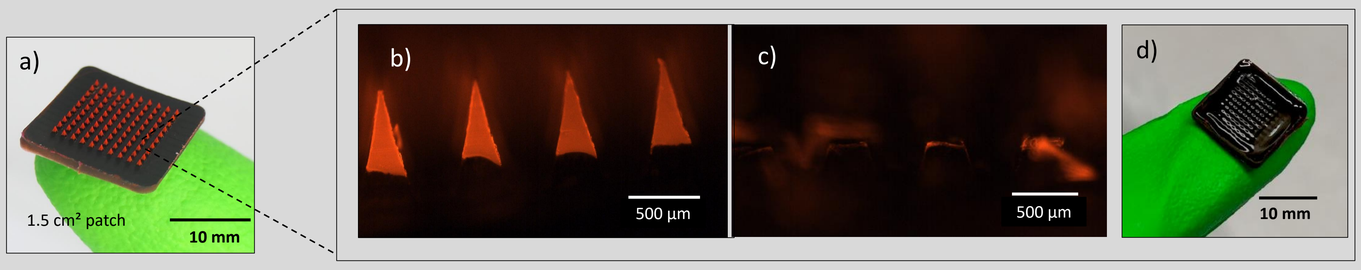


Figure 1. LBF and SPION loaded microneedle patch. a) and d) Digital photographs of the tips and the backing layer of the patch. The patches were inserted on bovine vaginal explant by hand. Fluorescent microscopy of before and after is shown in b) and c), where the LBF loaded tips have dissolved almost completely post 6 hours.

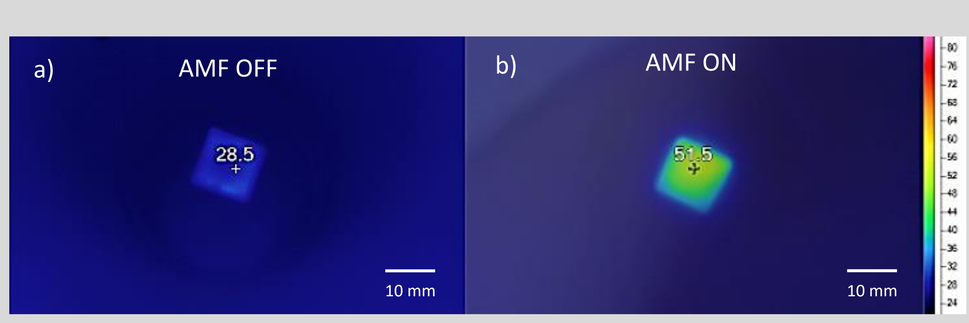


Figure 2. Infrared images of the microneedle patch a) Before the AMF was turned on and b) when AMF was turned on, the patch heats up to 51 °C in under 3 minutes.

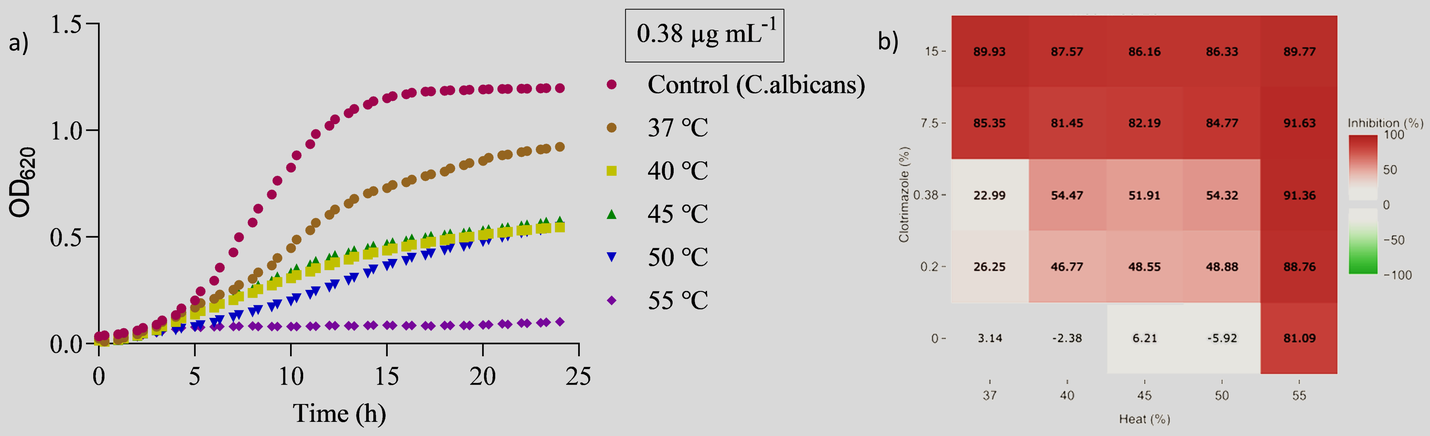


Figure 3. *In vitro* analysis of the fungal growth curve after having estimated the MIC and NIC of clotrimazole in Candida albicans. a) When the fungal suspension was heated, and when observed under UV at 620 nm, it is observed to be more susceptible to clotrimazole at NIC (optical density (OD) = *Candida* concentration) and b) inhibition efficiency against *Candida albicans* increases with the increase in both clotrimazole concentrations and heat.

Conclusions

- SPION loaded microneedles were successfully fabricated and demonstrated efficient heating in air, reaching temperatures up to 51 °C. Further hyperthermia testing needs to conducted *ex vivo* on excised vaginal tissue.
- Preliminary results show enhanced inhibition of *Candida albicans* when combining heat with clotrimazole. Further replicates and BLISS model analysis are ongoing to evaluate potential synergy or antagonism.

References

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