An MRI-Guided HIFU-Triggered Wax-Coated Capsule for Supertargeted Drug Release

Olha Wuerthinger[1], Simon Matoori[2], Maurizio Roveri[2], Peter Tiefenboeck[2], Annatina Romagna[1], Orpheus Kolokythas[3,4], Johannes Froehlich[1,2]

[1]Clinical Research Group, Klus-Apotheke, Zurich, Switzerland, [2]Institute of Pharmaceutical Sciences, Department of Chemistry and Applied Biosciences, ETH Zurich, Zurich, Switzerland, [3]Department of Radiology, Kantonsspital Winterthur, Winterthur, Switzerland, [4]Department of Radiology, University Washington Medical Center, Seattle, WA, USA

Introduction

Background:

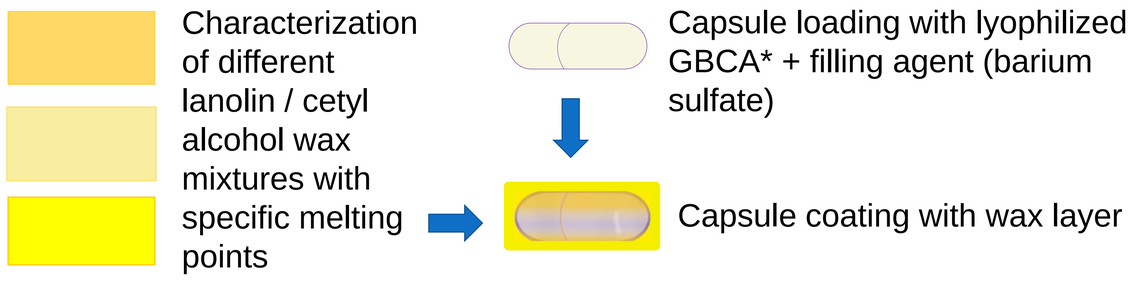
- In many diseases (e.g. non-metastatic solid gastrointestinal (GI) tumors, Crohn's disease) **current treatment strategies** involve **systemic** administration of drugs.
- **Spatially and temporally controlled drug release** reduces systemic **side effects** while simultaneously increasing the **drug concentration** at the required site.
- Currently no **galenic formulations** are known which are stable in GI fluids and allow for **externally controlled and monitored drug release** in the GI tract.

Aim: To develop a supertargeted drug delivery system (DDS) for personalized non-invasive therapy.

Property	Concept	Method
Stimuli-responsive DDS	Thermoresponsive system	Wax-coated capsule
Externally controlled trigger of drug release	Focused rise of temperature	High-intensity focused ultrasound (HIFU)
External monitoring of drug release	Imaging of T1-hyperintense signal due to drug release	Magnetic resonance imaging (MRI) + Gadolinium-based contrast agent (GBCA)

Methods

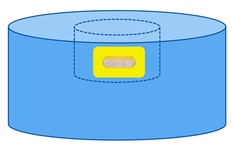
Development of wax-coated capsule:



* 0.2 mL gadoteric acid meglumine 0.5 mmol/mL, Dotarem®

MRI-guided HIFU-triggered drug release:

- MRI-guided HIFU is clinically validated for non-invasive thermal ablation of solid tumors (e.g. breast and prostate cancer).
- Externally triggered **highly localized temperature increase.**
- Applied HIFU pulse leads to melting of the wax-coating of the capsule: 200 W, 1195 kHz.



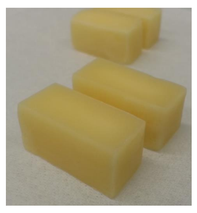
Wax-coated capsule in water-filled cavity of HIFU gel phantom

Philips Sonalleve MR-HIFU

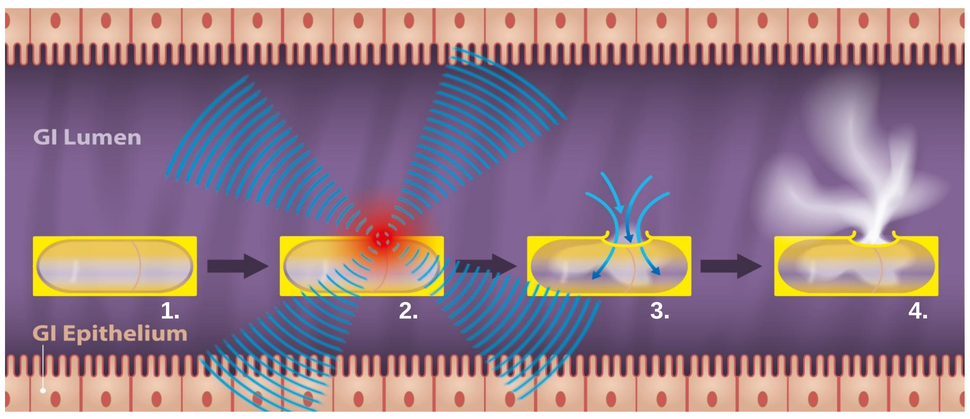
Results / Discussion

Development of wax-coated capsule:

- Most suitable wax mixture: lanolin/cetyl alcohol 1:1 (m:m)
  - mp = 43°C (stable at body temperature)
  - Highly resistant to simulated gastric and intestinal fluid



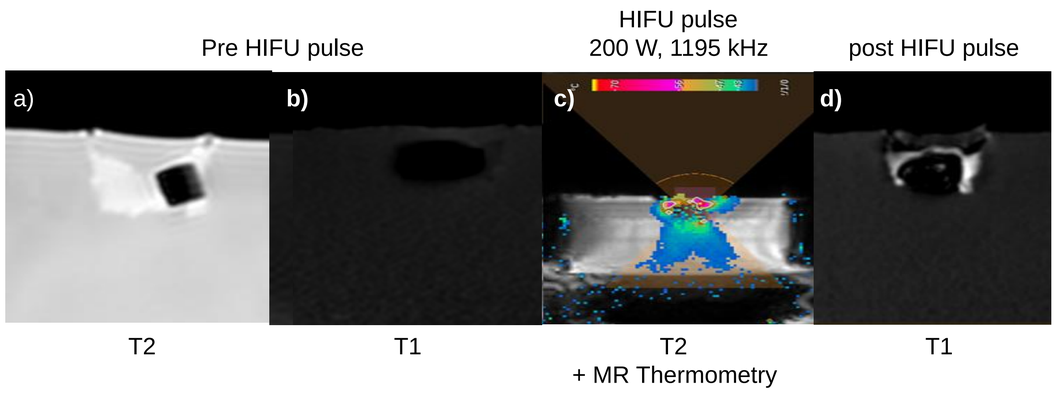
Schematic representation of the drug release:



1. The wax-coated capsule is **resistant to GI-fluids at body temperature** → no premature release.
2. **Melting of a focused hole into the wax coating** by an external **HIFU pulse**: 200 W, 1195 kHz.
3. **Water influx** from the GI lumen into the capsule.
4. Dissolution and **outflux of GBCA** through the hole in the wax-coating.

MRI-guided HIFU-triggered drug release:

Proof of concept for a novel application of MRI-guided HIFU for supertargeted drug release:



a) Localization of the capsule due to its T2-hypointensity on T2-weighted MR images.
b) Lack of a T1-hyperintense signal prior to the HIFU pulse shows that **non-hydrated** lyophilized **GBCA** is not T1-hyperintense.
c) Application of a **HIFU pulse** guided by T2-weighted MRI and temperature monitoring using MR thermometry.
d) The hyperintense T1 signal on T1-weighted MR images proves **outflux and hydration of GBCA** after the HIFU pulse.

Conclusion

- Development of a **thermoresponsive wax-coated capsule** for supertargeted drug release:
  - Stable at physiological conditions (body temperature, simulated GI fluids).
  - Releasing its cargo at T ≥ 43°C, promising non-invasive HIFU application.
- Proof of concept for the novel application of **MRI-guided HIFU** as an **externally controlled heat trigger for drug release.**
- Introduction of **MRI** as a method to **monitor the capsule and the release of its cargo.**

References

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