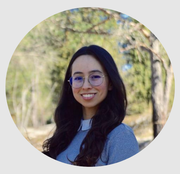
IntesTiny: Preclinical Evaluation of the Dynamic Biotransformation of Novel Nanomaterials for Inflammatory Bowel Disease



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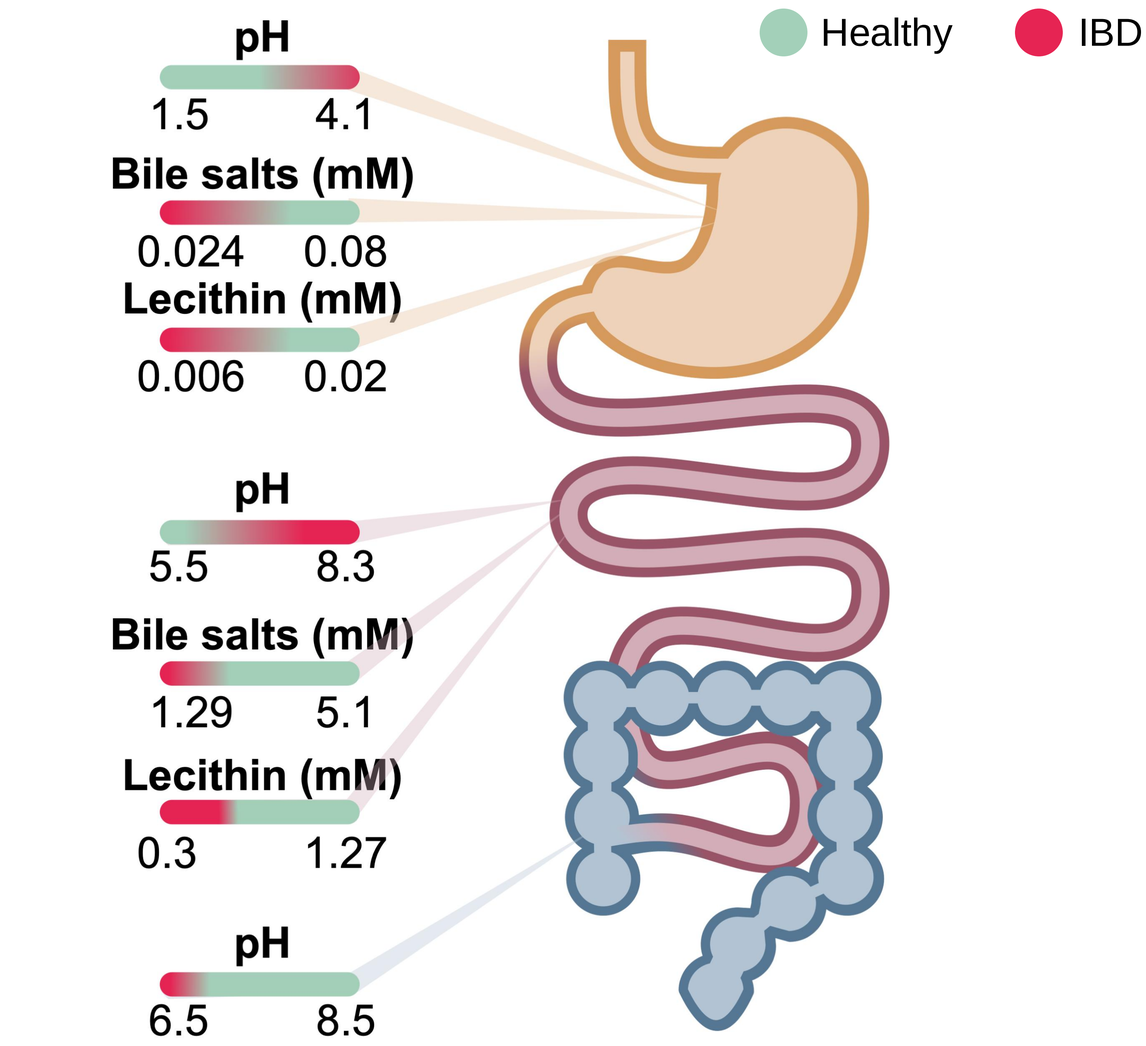

Figure 1. Changes in the gastrointestinal tract with IBD[2] (red color). To account for the heterogeneity of fluids among individuals, a design of experiments approach was employed to develop simulated fluids of the stomach, small intestine, and colon.

Microfluidic device development

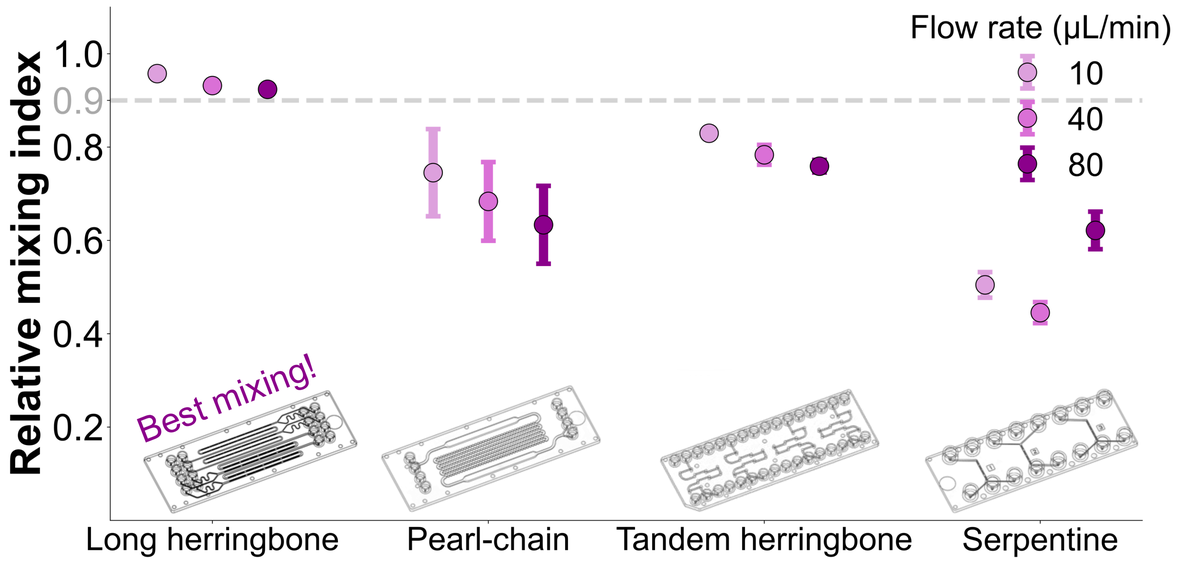

Figure 3. Comparison of the relative mixing index (RMI)[3] of four commercially available micromixers. The best micromixer was chosen for development of IntesTiny.

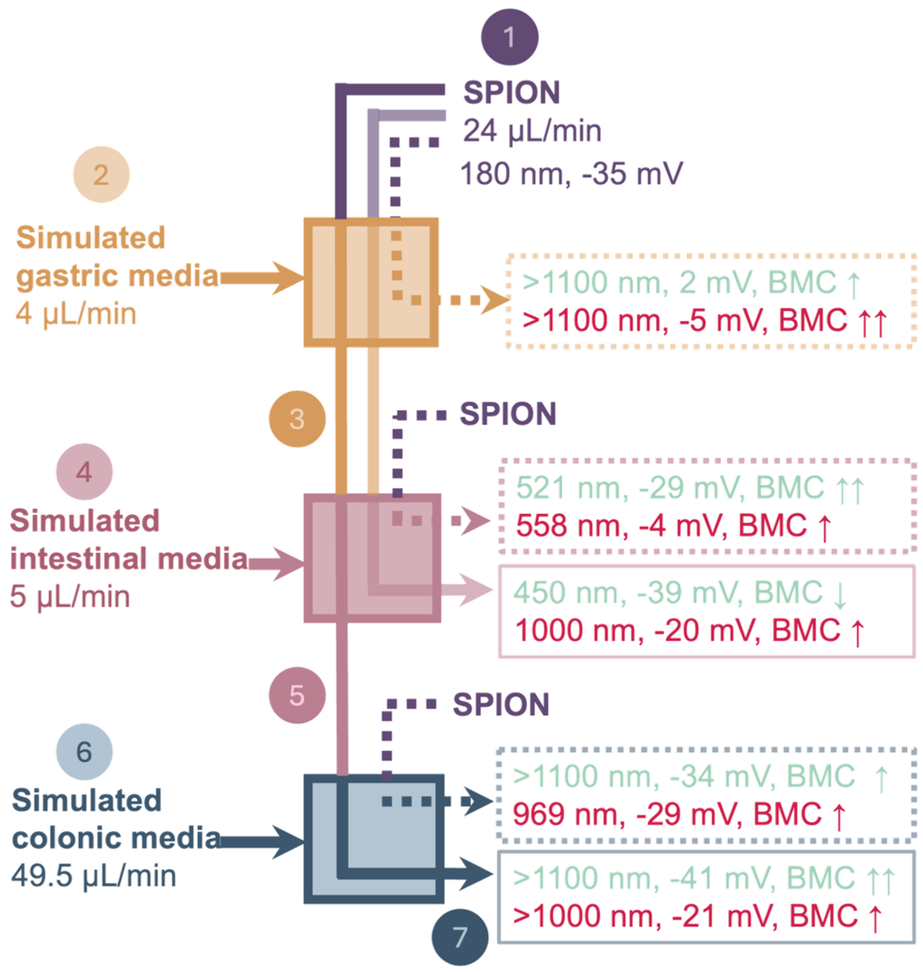

Figure 5. Schematic representation of IntesTiny simulating nanoparticle passage through the GIT. In the output, the hydrodynamic diameter d_{DLS} (nm), ζ-potential (mV), Total adsorbed biomolecular corona (BMC) ↑ increase or ↓ decrease compared to the amount of biomolecules in the previous stage, in the healthy (green) and IBD (red) state are reported.

[1]Barnes, C., et. al. (2020). ADC. 105(7): 671–676.
[2]Vinarov, Z., et. al.,. (2021). Eur. J. Pharm. Sci.. 1(162):105812.
[3]Hashmi, A., & Xu, J. (2014). SLAS Technology. 19(5): 488–491.

Introduction

Inflammatory bowel disease (IBD) is a chronic disease that affects more than 3 million patients in Europe[1]. Superparamagnetic iron oxide nanoparticles (SPION) can be used as orally delivered contrast agents for diagnosis of IBD by magnetic resonance imaging. However, the lack of in vitro methods to assess the nanoparticle's dynamic behavior in the gastrointestinal tract (GIT) hampers their translation to clinical use. The aim of the project is to develop a microfluidic device, **IntesTiny**, for mixing healthy and IBD-simulating fluids with nanoparticles to study the impact of fluid composition on nanoparticle stability and biomolecular corona formation in different GIT regions.

Nanoparticle characterization

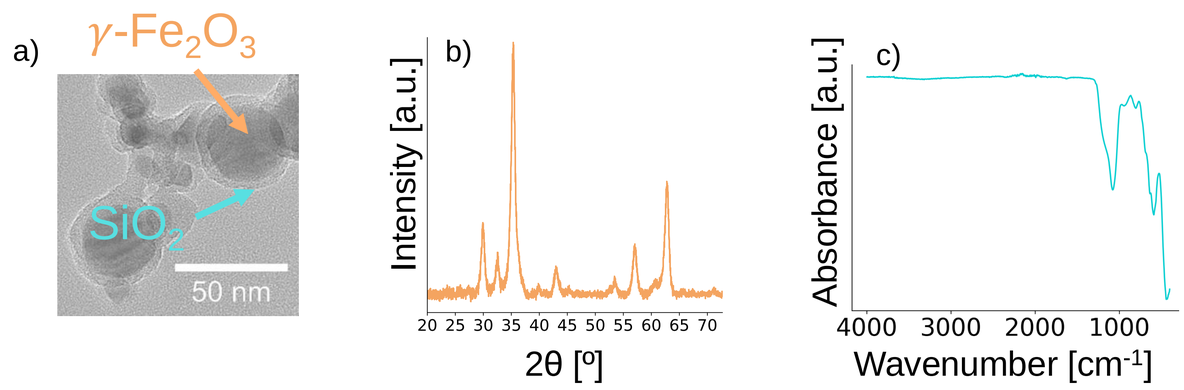

Figure 2. a) Micrograph of the silica-coated SPION. b) X-ray diffraction pattern confirms a maghemite phase. c) Fourier transform infrared spectroscopy confirms the presence of silica (peak at 1060 cm-1).

Nanoparticle dynamics in the microfluidic GIT

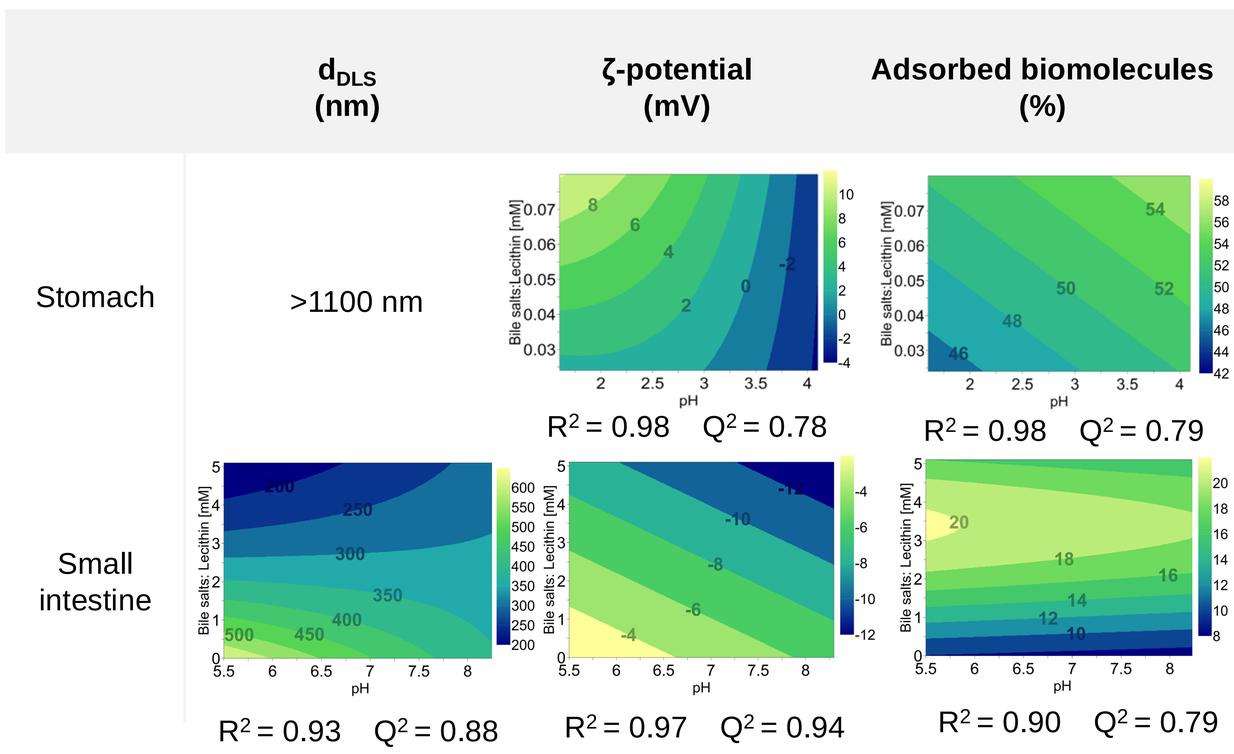

Figure 4. Contour plots of nanoparticle response to different levels of pH, protein content, lecithin, and bile salts. In the stomach compartment all hydrodynamic diameters were >3000 nm, while protein adsorption in sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was <2%. In the small intestine compartment, protein adsorption was <10% by SDS-PAGE at all conditions tested.

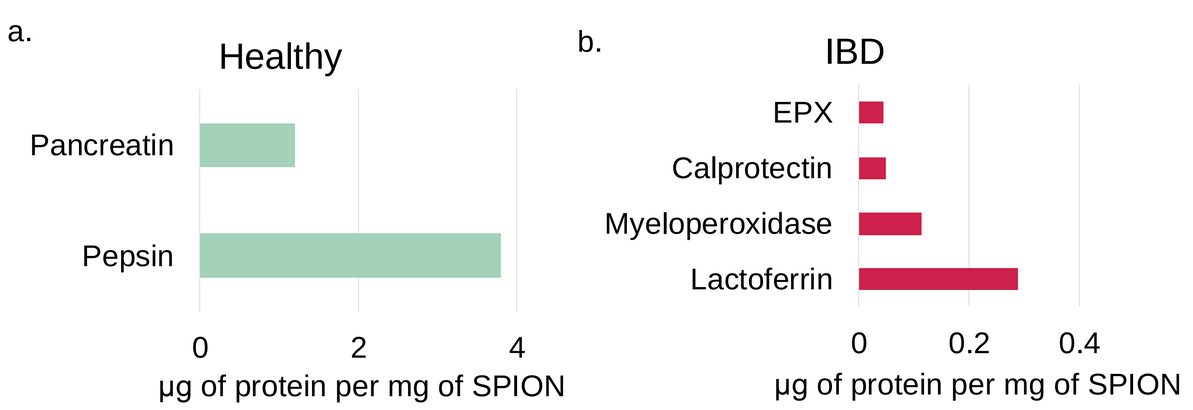

Figure 6. Composition of the hard protein corona (measured by SDS-PAGE) after the sequential exposure to gastric, small intestinal, and colonic media in simulated healthy conditions (a) and IBD-conditions (b).

- The long herringbone micromixer had the best relative mixing index and therefore was selected for the development of IntesTiny.
- In the gastric and small intestinal compartments, pH, bile salt, and lecithin levels influence the properties of the SPION.
- The physicochemical changes of the GIT fluids with IBD impact the surface charge, size, and biomolecular corona formation of SPION.
- IntesTiny can be used as a preclinical evaluation tool to characterize the dynamic biotransformation of nanomaterials.