Development of an innovative gastric and small intestinal human model simulating differential gastric emptying of real-size food particles and ileal microbiota

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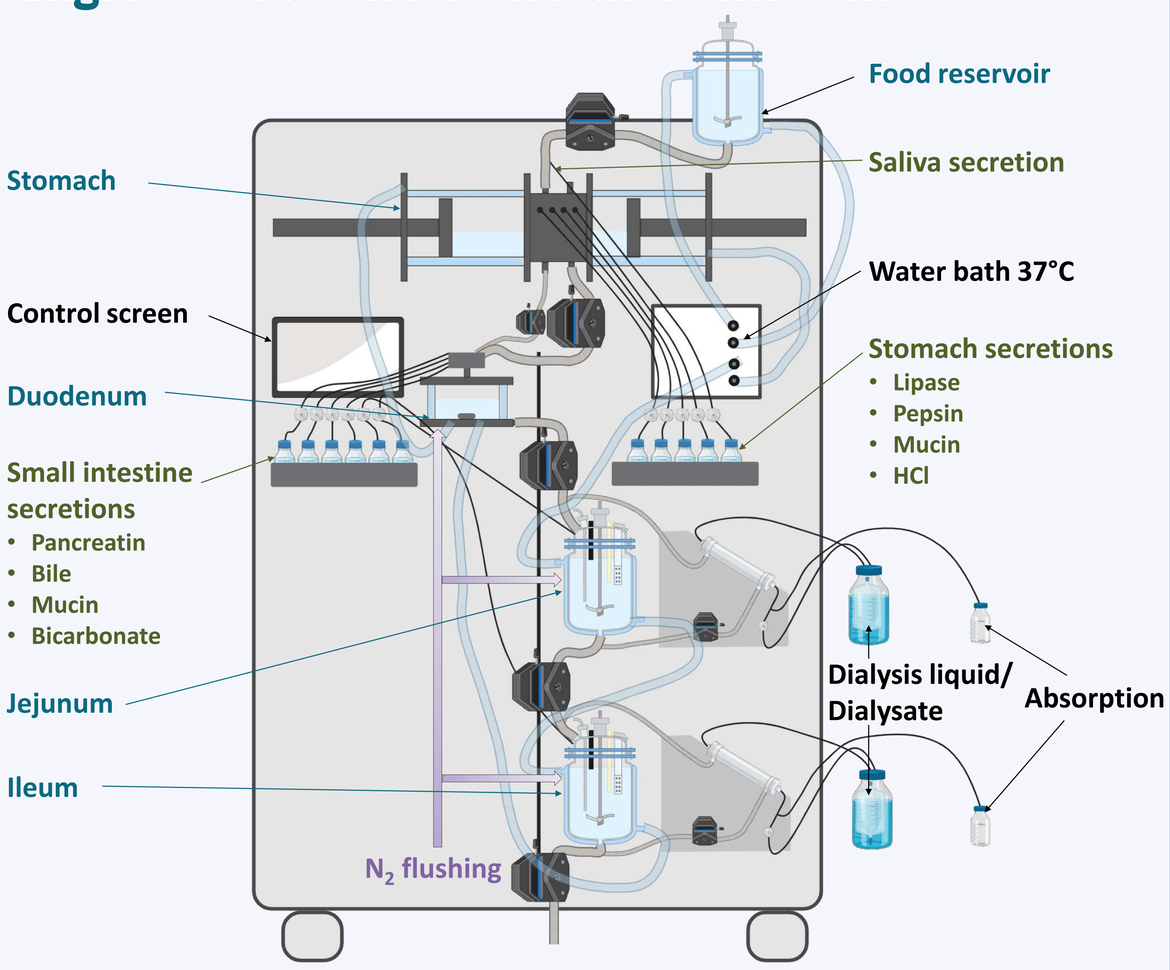
INTRODUCTION

Numerous studies have highlighted the key role of food structure in digestibility and nutrient bio-accessibility. Additionally, resident gut microbes in the upper digestive tract, particularly in the small intestine, are heavily assumed to play a key role in human nutrition and health, but are up to now understudied due to sample invasiveness.

In this context, the aims of this study are:

- Optimize a new dynamic and multicompartmental *in vitro* model of the human upper gastrointestinal tract able to handle real-size food particles
- Integrate in the model the resident microbiota in the ileal compartment
- Validate the model using a liquid meal digestion protocol, by following gastric and ileal deliveries and bio-accessibility of paracetamol as a model drug compound

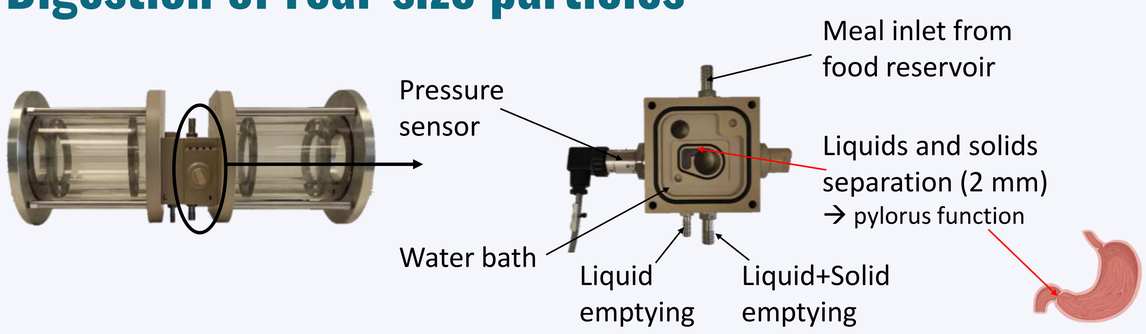
Engineered Stomach and Small Intestine



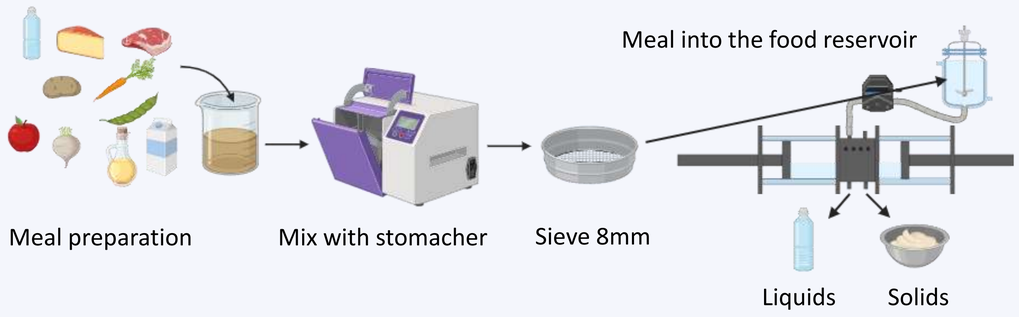
This new *in vitro* model reproduces, based on *in vivo* data, the main parameters of the human digestive tract, i.e.: body temperature; kinetics of gastric and intestinal pH; kinetics of gastric and ileal deliveries; transit time; oral, gastric, biliary and pancreatic secretions; passive absorption of nutrients and water; and anaerobiosis.

In a unique way, this model will also handle **food particles with realistic sizes and integrate resident microbiota in the ileal compartment.**

Digestion of real-size particles



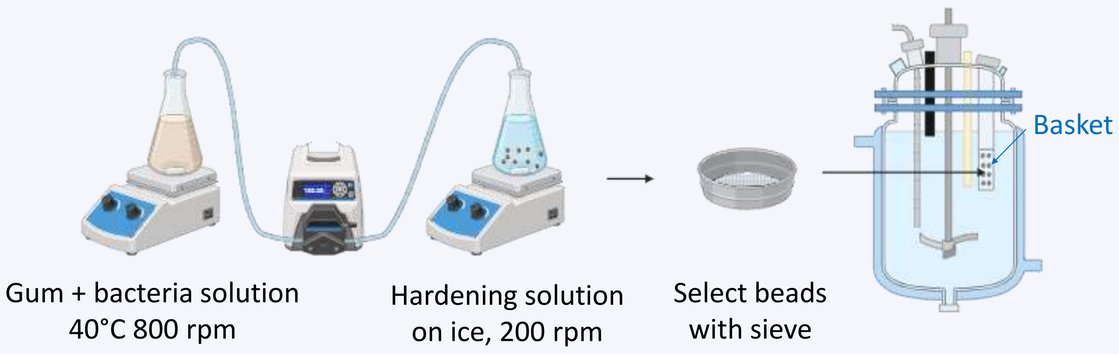
The **innovative structure** of the stomach allows **differential emptying of liquids and solids**[IV].



Three mixing protocols were tested: Ultra-Turrax producing a homogeneous puree with no distinguishable particles, stomacher leading to ~ 8 mm particles and no mixing which resulted in oversized particles causing clogging in ESIN. Stomacher crushing appeared suitable for both physiological relevance mastication and system technical compatibility.

[IV]M. Alric, & S. Denis, 2009. *Patent nW02009087314.*

Ileum microbiota



Beads in the basket of the ESIN ileum

Beads mean size : 5.43 +/- 0.23 mm

Beads basket capacity : 40 beads

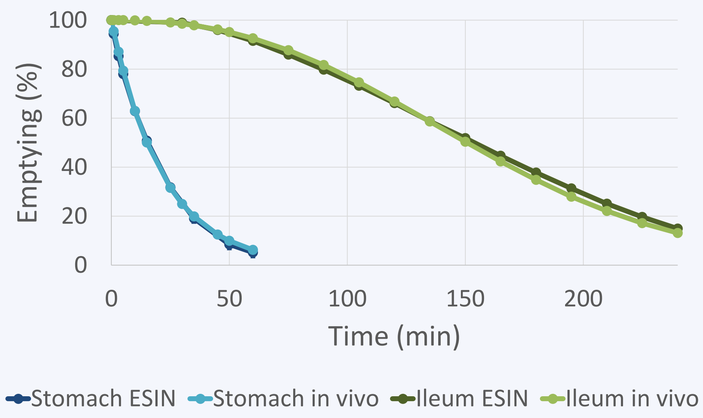
To **avoid microbiota wash out** in the ESIN model, bacteria will be immobilized in **gellan-xanthan beads**[V] and introduced into the basket of the ileum compartment.

This protocol is undergoing optimization using a single bacterial strain, but in the final implementation, beads will be colonized with a consortium of bacteria representative of the ileum microbiota or with a complex ileal-like microbiota derived from stool.

[V]G. Esmail, *et al.*, 2025

First fasted state validation experiments

Gastric and ileal liquid emptying

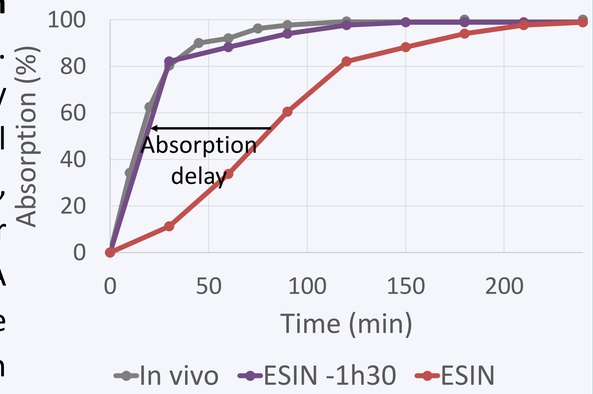


Transit was tracked using dextran blue as a **non-absorbable marker**. *In vivo* data were modeled using the Elashoff curve[I], showing good correspondence between *in vitro* results and *in vivo* data.

Stomach emptying (n=9) had a $T_{1/2}$ of 15 min, while ileum emptying (n=3) showed a $T_{1/2}$ of 150 min.

Paracetamol bio-accessibility

Paracetamol was administered with a glass of water and the **drug absorption** was followed in the jejunum and ileum. *In vivo* data were measured in salivary samples after ingestion of 1 paracetamol tablet with 250 mL water[II]. In ESIN (n=3), total cumulative absorption was slower than *in vivo*. According to FDA guidelines[III], modifications can be applied to *in vitro* data for comparison with *in vivo* results. When applying a 1.5-hour delay, *in vitro* absorption curve was similar to the *in vivo* one.



[I]J. Elashoff, *et al.*, 1982; [II]S. Souliman, *et al.*, 2006; [III]Food and Drug Administration, 1997

DISCUSSION

This study **validates a fasted state protocol** in the innovative gastric and small intestinal model ESIN, in relation to gastric and ileal emptying and bio-accessibility of a model drug. Other experiments are ongoing in order to validate the digestion protocol of a **real meal** and an **immobilization process for gut microbes** before introduction in the ileal compartment.

In a near future, ESIN will help to move towards a **better understanding of the role of food structure and ileal microbes in human or animal nutrition and health**, particularly in terms of **food matrix-microorganism interactions** and **impact of intestinal microbiota** on macronutrient digestibility or drug bio-accessibility.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