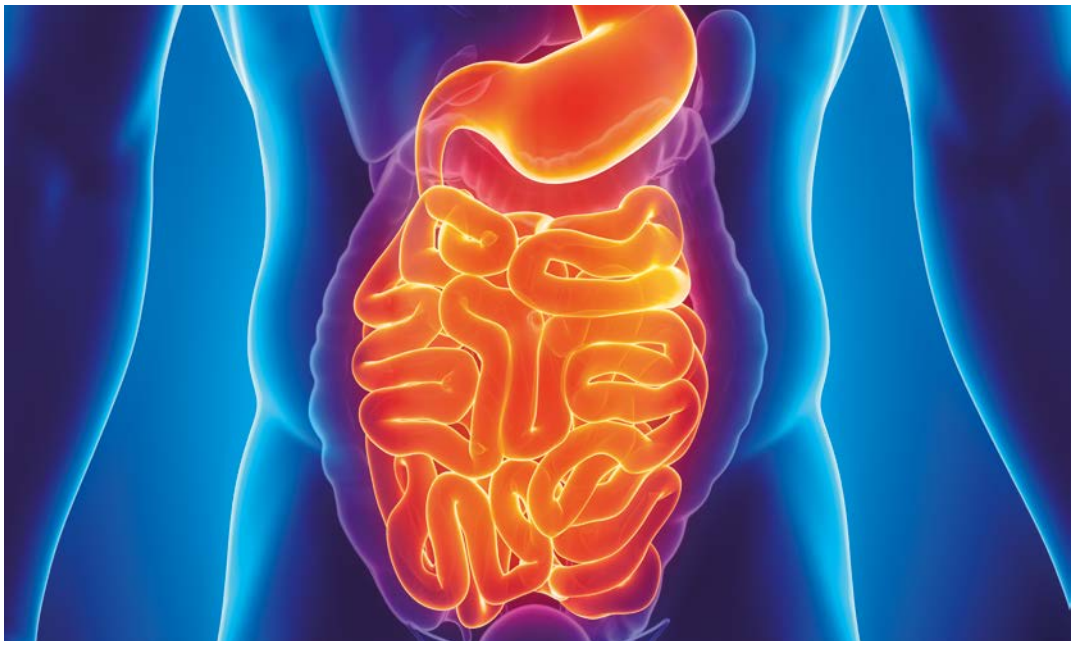
InTESTine™

STUDY PROCESSES THAT DETERMINE INTESTINAL ABSORPTION



TNO innovation for life

In the development of pharmaceutical and nutritional products an accurate prediction of the oral fraction absorbed in humans is essential. The bioavailability of a compound at the target site co-determines the efficacy of the active compound. Current *in vitro, in silico* and *in vivo* models are often not sufficient to investigate. TNO has developed InTESTine™, a new *in vitro* intestinal model using healthy porcine intestinal tissue, which is applicable to study these various processes that determine the oral fraction absorbed.

One of the unique features of InTESTine™ is the opportunity to study multiple intestinal segments (duodenum, jejunum, ileum & colon) in parallel, under controlled conditions, in order to study regional differences in absorption. This is important, as the morphology and function of the intestinal tract changes from duodenum to colon with respect to thickness of the mucus layer, height of the villi, pore size of the tight junctions, expression levels of transporters, receptors and/or metabolizing enzymes. Additionally, due to the presence of the mucus layer, intestinal processes can be studied following exposure to digested samples, and in the absence or presence of microbiota. This clearly demonstrates the additional value of InTESTine™ compared to monolayer cultures (e.g. Caco-2 cells) in order to study absorption, metabolism and/or food-drug and excipient-drug interactions of orally administered compounds.

YOUR ADVANTAGE

- Tailored made study design with various relevant opportunities, as TNO has broad expertise in intestinal physiology, active drug transporters, immune response and microbiome analysis;
- You can study processes that determine oral drug absorption *in vitro* across multiple and various intestinal regions (duodenum to colon);
- InTESTine™ is well applicable for screening drug toxicity (safety), early immune responses, and/or endocrine responses.

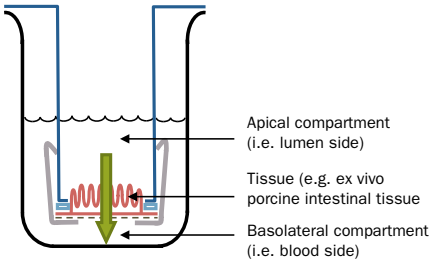


Figure 1. Schematic representation of InTESTine™ system.

FEATURES OF INTESTINE™

Within the InTESTine™ system, freshly isolated healthy intestinal tissue from pigs is used. The gastrointestinal tract of pigs, like humans omnivorous, show great similarities with the human GI tract. The main advantage of using pig tissue is the high availability along the whole GI tract. The easy set-up and horizontal mounting of tissue in InTESTine™ (Figure 1) enables the system to be incubated in a humidified oxygenated incubator at 37°C on a rocker platform thereby reducing the unstirred water layer, evaporation and possible foaming. The horizontal mounting of tissue also enables the direct contact of test compounds with the epithelial tissue. Multiple devices can easily be arrayed allowing medium throughput analyses of your compound of interest in the InTESTine™ platform in a cost-effective way. In addition, the device is generated from disposable (glass) material, which reduces nonspecific binding of the compound of interest and risk of contamination of the mounted device.

Compound characteristics	Porcine vs Human (r^2)	Caco-2 vs Human (r^2)
Passive transport	0.73	0.66
Active transport	0.78	0.45

Table 1. Coefficient of determination (r^2) between P_{app} values of 20 compounds determined in InTESTine™, human Ussing chamber and Caco-2 cell Transwell system.

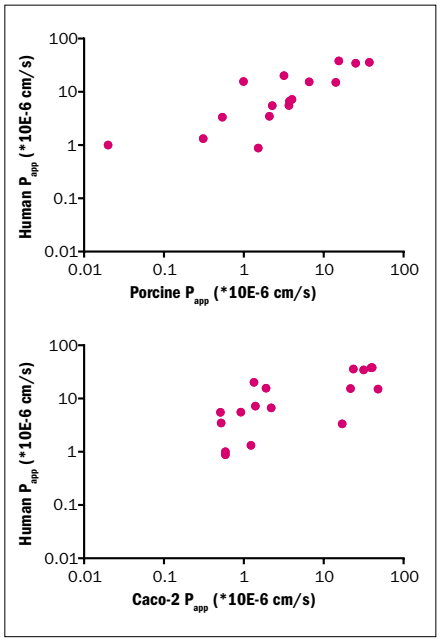


Figure 2. Evaluation of porcine InTESTine™ system in comparison to human Ussing chamber and Caco-2 cell Transwell system. Data present log apparent permeability (P_{app}) values of 20 compounds determined across A) porcine intestine mounted in InTESTine™ and B) monolayers of Caco-2 cells versus log P_{app} values of human intestine mounted in Ussing chamber (based on literature data).

COMBINED SERVICES

InTESTine™ services can be easily combined with other platforms and techniques, including:

- Microbiome analysis;
- *In vitro* and *in vivo* PK and immune models;
- *In silico* PBPK modeling of absorption, first pass metabolism and/or bioavailability;
- TNO dynamic gastraintestinal model (TIM, stationed at our full subsidiary TNO Triskelion), which highly simulates gastraintestinal luminal proccesses (collected samples can be dosed to InTESTine™)

REFERENCES

Westerhout et al., European Journal of Pharmaceutical Sciences 63 (2014) 167–177

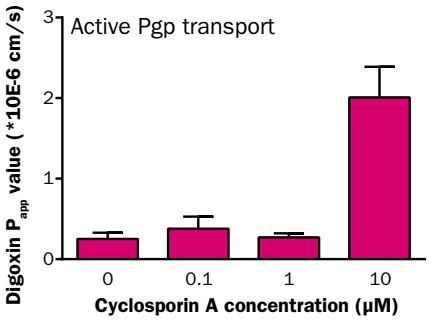


Figure 3. Intestinal apparent permeability (P_{app}) of digoxin, a substrate for active efflux transporter (Pgp) in InTESTine™ system. Cyclosporin A, a known inhibitor of Pgp, increases the permeability of digoxin towards the basolateral side.

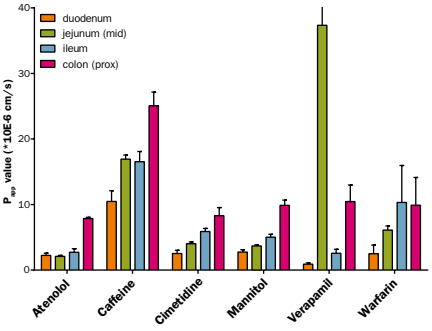


Figure 4. Regional intestinal apparent permeability (P_{app}) of several compounds across porcine duodenum, jejunum, ileum, and colon tissue mounted in InTESTine™.

TNO.NL

TNO HEALTHY LIVING
TNO initiates technological and societal innovation for healthy living and a dynamic society.

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