

TIM GASTROINTESTINAL SYSTEMS



TNO innovation
for life

TNO's patented *in vitro* gastrointestinal model TIM offers rapid insight into the release, solubility and availability for absorption of pharmaceuticals within the gastrointestinal tract. This well-validated and accurate system has a much greater *in vivo* predictive value than typical *in vitro* dissolution assays. Additionally, it is a cost-effective alternative for human and animal trials, accelerating the process of product development.

Within the gastrointestinal tract, digestion is characterized by a series of events including food and water intake, the subsequent release of digestive enzymes and fluids, mixing by peristaltic contractions, and transit through the stomach and intestines. These kinetic processes are responsible for the breakdown, interaction and uptake of nutrients and pharmaceutical agents.

ACCURATE SIMULATION

The computer-controlled gastrointestinal model TIM accurately simulates these physiological processes and conditions within the gastrointestinal tract. The TIM system consists of several compartments which are interconnected by valves regulating gastrointestinal transit. The system mimics the body's temperature and peristaltic movements.

Acidity and electrolyte concentrations in the system are dynamically monitored and regulated, as are the presence of swallowed saliva and the 'secretion' of gastric acid and enzymes, pancreatic juice with enzymes, and bile salts.

The TIM-1 system represents the gastrointestinal tract from stomach through small intestine, while TIM-2 simulates the large intestine. Both models have been validated in comparison to *in vivo* studies and used to evaluate a large number of drugs from all BCS classes, administered in a wide range of formulations and under various physiological conditions (e.g. fasting state versus fed state). Upon request, TNO can supply a track record of the drugs and formulations that have been successfully studied in TIM.



TIM-1



TIM-2

COST-EFFECTIVE

TIM's main advantage is that it combines an accelerated process of drug development with increased *in vivo* predictive value. A wide range of physico-chemical properties of formulations and drugs can be investigated in the model, including drug product solubility, coating stability, formulation release profile, availability for absorption, as well as drug-drug and drug-nutrient interactions. With this information, companies can make better informed decisions concerning which compounds and/or formulations are most promising for further *in vivo* studies or to refine clinical trial design.

As a physiologically relevant *in vitro* model, TIM experiments are free from the regulatory and ethical constraints associated with animal and human clinical trials. One could even work with (potential) toxic compounds or disease-causing bacteria (under containment conditions) without harming animals or humans.

MANY APPLICATIONS

Using TIM, TNO can conduct a detailed analysis of the release, solubility and bioaccessibility profile of a compound, as well as other physico-chemical properties or pharmaceutical interactions during gastrointestinal transit. Each compartment can be studied separately, measuring even relatively small changes in bioactive components. The model can be adapted to a wide range of target populations, such as infants, young adults, seniors and patients with impaired gastrointestinal conditions. TIM can also be used to model the gastrointestinal physiology of animals, such as dogs and pigs.

For over a decade, the TIM systems have been used successfully, and study results have been described in over 80 scientific, peer-reviewed publications. Data from the TIM systems have been accepted by several regulatory agencies, including the US Food and Drug Administration (FDA). A list of (peer-reviewed) publications is available on request.

TRACK RECORD

To date, TNO has tested over 90 different active compounds in over 240 different formulations in the TIM-1 system. Most of these were evaluated under fasted, as well as fed state conditions, with or without a FDA recommended high fat meal matrix. Most of these tested compounds were poorly water soluble, while 70% were lipophilic. Divided by BCS class I + III and class II + IV, the ratio was approximately 3:7. In a number of cases the compounds and formulations have been tested under specific pathological gastrointestinal conditions. In TIM-2, both in isolation and in combination with TIM-1, TNO has tested more than 25 different compounds and formulations on their bioaccessibility from the colon and/or on bioconversion to the activated form by the colon microbiota. In 60% of these experiments, TNO has also investigated the influence of drugs on the composition and metabolic activity of the microbiota after single or repeated dose.

TNO collaborates with Seventh Wave Laboratories to perform TIM-1 studies in North America

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COMBINED SERVICES

TIM-1 and TIM-2 services can be combined with other expertises, including:

- › cell cultures and intestinal segments, to study intestinal cell transport, metabolism and specific functions;
- › *in silico* modeling, to predict plasma levels after single dosage or during long-term oral intake;
- › pharmacokinetic studies (ADME) and pharmacodynamic studies.

FURTHER INFORMATION

For further information on TNO, TIM applications or scientific publications, please contact us.

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TNO HEALTHY LIVING

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

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