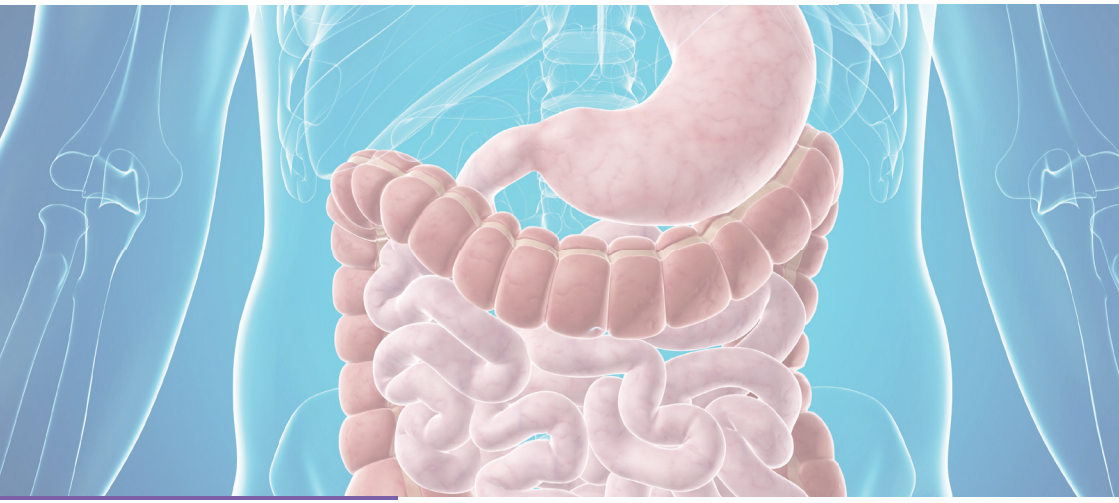
TRISKELION
RESEARCH FOR BETTER LIVING

A TNO COMPANY



NEW GENERATION

A HIGH-END DISSOLUTION AND DIGESTION APPARATUS

As part of oral drug development, reliable scientific data are needed about the transit of the dosage form through the gastrointestinal tract and release and dissolution of the API in the gut. This should preferably be investigated in a time- and cost-efficient way. Triskelion fulfills these requirements by offering gastrointestinal testing with the **T**NO gastro**I**ntestinal **M**odels (TIM). The TIM-1 and tiny-TIM systems simulate the dynamic conditions in the stomach and small intestine, whereas the TIM-2 system simulates the large intestine.

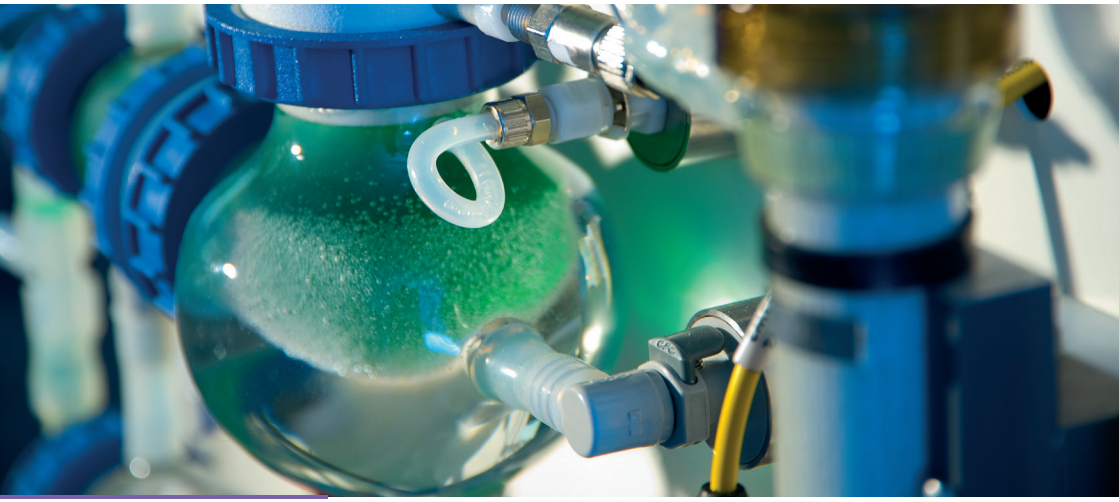


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Figure 1. tiny-TIM system.

1. INTRODUCTION

Innovation is crucial within the pharmaceutical- and biotech industry. Triskelion supports your innovation process by science-based expertise, high-end facilities and state-of-the-art solutions.

New drugs or reformulated drugs need to have optimal efficacy and a well targeted delivery of active ingredient to minimize the necessary dose and reduce adverse side-effects.

The intake of food and drinks may also have an effect on your formulated drug.

As a stakeholder in the pharmaceutical research and the development of oral dosage forms, you would like to gather information about the gastrointestinal behavior of formulated and unformulated active pharmaceutical ingredients (APIs) in a time-efficient and cost-effective way.

For this reason *in vitro* models that aim to mimic the conditions in the gastrointestinal (GI) tract are widely used by the feed, food and pharma industries.

The benefits of these *in vitro* models are:
- Simplified use and increased reproducibility vs *in vivo* studies
- Higher throughput (faster and more cost-efficient)
- No ethical constraints

A model should be as simple as possible, but simplifying also narrows the use and predictive quality of the results for the *in vivo* situation. The complexity of the real-life gastrointestinal tract requires dynamic models that simulate the successive conditions in the stomach and intestine. Since 1992 TNO and Triskelion (The Netherlands) have been developing and validating dynamic, multi-compartmental, computer-controlled laboratory models that simulate the gastrointestinal tract of humans and some mono-gastric animals (TIM systems).

This TIM technology is widely used in contract research. From the food, feed and pharmaceutical industries to scientific research, product development, claim support and international collaboration projects, the TIM systems have clearly proven their value. The predictive quality of the TIM systems has been published in over 180 articles in peer-reviewed international journals (list available on request).

In response to demand, we have designed a TIM system (tiny-TIM) that can be used by both industrial and academic researchers as an on-site laboratory apparatus. This tiny-TIM system closely mimics the events in the lumen of stomach and small intestine in an accurately controlled way (details are given in this brochure).

Among others, this tiny-TIM system can be used for:
- Dosage form testing on the release, dissolution and bio-accessibility of APIs under fasted and fed-state conditions
- Bio-equivalence studies
- Drug–drug and drug–nutrient interactions
- Proof of concept studies

Samples are collected during the tiny-TIM experiments in time for analysis, giving data on the availability for absorption through the gut wall (bio-accessibility) of compounds during gastrointestinal digestion and transit. The accurate and reproducible simulation of the gastrointestinal conditions means that duplicate experiments are sufficient to reliably predict the *in vivo* situation.

Figure 1.

2. tiny-TIM APPARATUS

The tiny-TIM system consists of three separate modules:

- A module that contains the gastro-intestinal compartments and its control unit
- A dispensing module with syringe pumps for the accurate distribution of the digestive fluids, and
- A sampling module for automatic sampling of the filtrate that contains the released, digested and dissolved compounds (Fig. 1)

General features:

- Table-top modules
- Simple and user friendly operation
- Software controlled system operation
- Pre-defined protocols
- Low labor intensity
- High accuracy and reproducibility
- Automated, volume-controlled sampling of filtrate
- Availability of standardized consumables (e.g. reagents, spare parts)

Figure 2. Gastrointestinal module with computer control.

2.1. GASTROINTESTINAL MODULE

The gastrointestinal module (Fig. 2) contains the gastric and small intestinal compartments, the computer with display, and the control and registration equipment.

2.1.1 COMPARTMENTS IN THE GASTROINTESTINAL MODULE

ADVANCED GASTRIC COMPARTMENT

The advanced gastric compartment (TIMagc) allows realistic simulation of gastric shape and motility. This serves your particular interest when gastric behavior of study compounds, such as phase separation and phase-dependent gastric emptying, is part of the experiment. For pharmaceutical research, the TIMagc allows the behavior of dosage forms to be studied under realistic gastric shear and pressure forces, and interaction with meal compounds. The TIMagc is described in more detail (including pH and secretion profiles) by Bellmann et al. (2016).

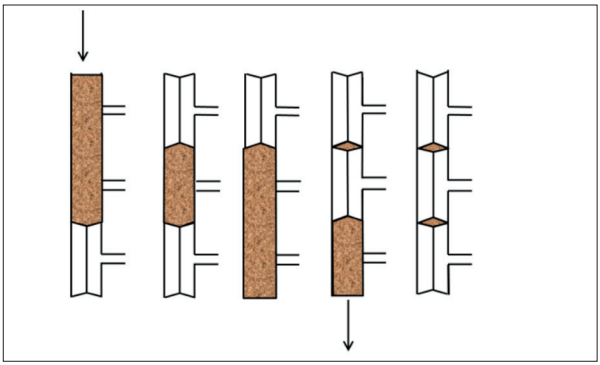

Figure 3. Peristaltic valve pump (PVP) showing transport of gastric content into the intestinal compartment.

PYLORIC VALVE

A computer-controlled peristaltic valve pump (PVP, Fig. 3), simulating the pyloric sphincter, transports the gastric content into the small intestinal compartment by peristaltic movements. The PVP allows accurate and controlled emptying of the gastric content, whether it contains particles or not.

SMALL INTESTINAL COMPARTMENT

The small intestinal compartment simulates the transit of the meal through the small intestine. Bile and pancreatin are secreted at true-to-life flow rates, resulting in physiological luminal concentrations. Bicarbonate is added to control the intestinal pH. The content is mixed by peristaltic movements and flushed through a hollow fiber-membrane unit to remove digested and released compounds that are small enough to pass through the semi-permeable membrane.

The type of hollow-fiber module can be selected on the basis of the compounds being studied. A dialysis module is used for the removal of water-soluble compounds from the intestinal lumen, while a filtration unit is used to remove mixed micelles that contain lipophilic compounds (e.g. fatty acids and lipophilic nutrients and/or pharmaceutical ingredients).

The unique membrane system ultimately allows the measurement of the bio-accessible fraction.

The peristaltic movements are accurately controlled by modulating the pressure on the water circulation (at body temperature) in the space between a flexible wall and a glass jacket. Maximum pressure is controlled by sensors in the water circulation.
The small intestinal compartment as part of the tiny-TIM system has been described previously in various peer-reviewed publications (see references).

Figure 4. Monitor screen showing the user interface.

2.1.2. COMPUTER CONTROL

The computer, which has a 12-inch touch-screen monitor, is placed in a separate compartment of the gastrointestinal module. The placement of the monitor and use of the touch-screen buttons allow easy and ergonomic operation of the tiny-TIM system.

The software focuses on easy use of the system through the automation of operations. The user interface structure takes the operator through the process step by step, reducing the risk of operating mistakes.

The following relevant process parameters are shown on the monitor screen (Fig. 4):

- Gastric pressure
- pH values (numerical and graphical)
- Temperatures (numerical and graphical)
- Volumes of the compartments
- Volumes of secreted digestion fluids
- Number of pulses by peristaltic valve pump (pyloric valve)

Figure 5. Dispensing module.

Prior to an experiment, a protocol file is selected that contains the data to simulate specific, realistic gastrointestinal settings. Each protocol file is accompanied by the related laboratory procedures to prepare the gastrointestinal fluids and Excel templates for data processing.

Triskelion supplies documented read-only protocol files for e.g. human (adult/infant), dog, pig, or pre-ruminant calve conditions, related to age and type of meal. During the process all relevant process data are logged, time stamped and protected to support quality control and reporting.

2.2. DISPENSING MODULE

The dispensing module (Fig. 5) pumps the secretion fluids into the gastrointestinal compartments and fresh filtration/dialysis fluids from/through the membrane units. The control system in the gastrointestinal module enables a syringe pump for each fluid to dispense with a high level of accuracy. The use of disposable 100 mL syringes with graduation allows direct visual monitoring of the dispensed volumes. The syringes containing enzymes are cooled.

Figure 6. Sampling module (number and size of sampling bottles is flexible).

2.3. SAMPLING MODULE

The sampling module (Fig. 6) is used to collect filtrate or dialysis fluid from the hollow fiber unit attached to the small intestinal compartment. All sampling bottles are placed in a holder on top of a balance. Sampling bottles are selected by moving the fluid outlet with an x/y system. The samples are pumped using a controlled FMI® pump into the designated sampling bottle to meet the pre-determined weight of each sample. Different holders can be used to allow various numbers of bottles and sampling sizes. The holder with bottles is placed on a drawer to allow easy access to the bottles from the front.

2.4. DIMENSIONS

- Gastrointestinal module:
  62 x 100 x 50 cm (w x h x d)
- Dispensing module:
  45 x 45 x 50 cm (w x h x d)
- Sampling module:
  45 x 55 x 50 cm (w x h x d)

3. REFERENCES

DEVELOPMENT OF TIMagc:

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APPLICATION OF tiny-TIM IN PHARMA RESEARCH:

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