

Chapter 4

Dynamic Digestion Models: General Introduction

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Abstract The first section of this chapter has focused on static digestion models and their specific applications. Whilst these static models have many advantages, they mainly function to mimic the biochemical processes in the gastrointestinal (GI) tract and usually use a single set of initial conditions (pH, concentration of enzymes, bile salts, etc.) for each part of the GI tract. However, this simplistic approach is often not a realistic simulation of the more complex in vivo conditions, where the biochemical environment encountered is constantly changing and physical parameters such as shear and grinding forces can have a large impact on the breakdown of larger food particles and the release of nutrients. Several dynamic digestion models have been developed in recent years to address these complex aspects of digestions, and four of these dynamic models will be presented in more detail in the following subchapters. This introduction will provide a brief overview of how the aspects of geometry, biochemistry and physical forces have been addressed in these and other dynamic digestion models.

Keywords Dynamic model • Digestion • GI tract • In vitro

4.1 Geometry

The human gastrointestinal tract consists of distinct compartments of differing shapes, sizes and orientations. These need to be considered when designing a realistic dynamic model. The stomach has a shape of an expanded J, with food entering from the esophageal sphincter at the top and eventually being released through the pylorus at the bottom. During digestion, body position may have an influence on some aspects of gastric digestion, especially gastric sieving of larger particles and pharmaceuticals. Three main approaches have been followed in the design of the models' gastric compartments, each with their own advantages and disadvantages: vertical alignment, horizontal alignment and beaker. Vertical alignment of the

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K. Verhoeckx et al. (eds.), *The Impact of Food Bio-Actives on Gut Health*,
DOI 10.1007/978-3-319-16104-4_4

gastric model allows phase separation to occur during digestion, as in vivo, but has the disadvantage of gravity influencing the sedimentation of larger particles towards the bottom opening (examples include the Dynamic Gastric Model [DGM, Chap. 6] and the Human Gastric Simulator [HGS; Chap. 7]). Horizontal alignment may be more suitable for the simulation of gastric sieving, but it does not provide a realistic representation of the low mixing environment of the gastric fundus (for example: TNO Intestinal Model [TIM-1, Chap. 5]). A stirred beaker is used in some models and is reminiscent of most static models (e.g. the DIDGI system [Chap. 8], and the in vitro Digestion System [IViDiS; Tompkins et al. 2011]). In a newer version of the IViDiS, Campbell et al. (2011) report the use of a molded, elastic stomach construct which more closely resembles the shape and size of the human stomach and is designed to mimic gastric peristalsis through the use of external rollers.

In contrast to the stomach, the peristaltic movements and tube-like structure of the small intestine may reduce the impact of body position on its function. Several dynamic digestion models use a horizontal, tube-like alignment to represent the small intestine. In these models, the peristaltic movements of the small intestine are simulated either by alternating pressure on the flexible wall of the compartment (TIM-1) or constrictions within the wall of the compartment (IViDiS). Other models use one or more thermostated beakers to simulate the small intestine (e.g. DIDGI-system; SHIME model, Chap. 27).

The design of the stomach and intestinal parts of digestion models has a direct impact on the physical forces exerted on the chyme, and how realistically the model simulates in vivo shear forces.

4.2 Physical Forces

Whilst passing through the stomach and small intestine, food particles and drugs are subjected to physical shear and grinding forces as well as pressure exerted by peristaltic movements. This is particularly true in the fed state within the stomach: During a meal, a complex mixture of masticated food bolus enters the fundus of the stomach where it may reside for several hours, depending on meal volume and caloric content. Within the fundus only gentle mixing occurs, whereas closer to the antrum peristaltic waves strengthen and the bolus is subjected to strong mixing and shear. The complex physical forces exerted by the GI tract are not well simulated by a stirred beaker approach; therefore the geometry of some dynamic models (see above) has been designed in such a way as to simulate these physical forces. Three notable examples are the HGS, the DGM and the TIM-1 (TNO's advanced gastric compartment), each of which has undergone validation of the physical forces exerted on the food bolus.

The Human Gastric Simulator's (Chap. 7) vertically aligned, cylindrical gastric compartment is periodically squeezed by the action of Teflon rollers on its flexible wall. These rollers impinge the compartment successively more towards the bottom, thereby simulating stronger forces nearer the antrum of the stomach. Kong and

Singh (2010) validated the model by measuring the pressure exerted on a rubber bulb within the compartment, and these pressures were found to fall within the range of mechanical stresses reported in literature for the human stomach.

The Dynamic Gastric Model (Chap. 6) consists of two connected compartments, simulating the fundus/main body and the antrum. Within the antral part, the food bolus is repeatedly passed through a flexible disc (annulus) to simulate the mixing and shear stresses encountered during antral contraction waves (ACWs) *in vivo*. Vardakou et al. (2011) validated these forces by comparing the mean breaking times of agar beads in high- and low-viscosity meals within the DGM, to the mean breaking times of beads in an equivalent *in vivo* study (Marciani et al. 2001a).

The TIM advanced gastric model (Chap. 5) simulates ACWs by modulating the pressure within a water jacket surrounding the antral compartment. Pressure profiles within this compartment were measured using a pressure-measuring capsule and compared to *in vivo* gastric pressure profiles (see Sect. 5.5).

4.3 Biochemistry

Dynamic digestion models, like static models, are built to mimic the biochemical environment of the compartments of the GI tract. Many of the considerations highlighted in the earlier sections of this chapter therefore apply to dynamic models as well: What concentrations of which enzymes, bile salts and phospholipids should be used? Can porcine, bovine or fungal versions of enzymes be used? Is it better to use complex mixtures (e.g. pancreatin) or individual, purified enzymes? At what pH should digestion take place? How long should a given meal reside in the stomach?

In contrast to static models, however, the exact conditions within the different compartments of a dynamic model will change over time to simulate the *in vivo* digestion processes. Dynamic digestion models generally have a number of different digestive secretions which are added to the compartments of the model over time. This addition can either follow a steady secretion rate (e.g. the simulated gastric juice of HGS is added at a rate of 2.5 mL/min), or it can follow a pre-programmed pattern allowing the rate to change over time (e.g. in the TIM-1 model), or it can be programmed to change in response to other parameters, such as the fill volume of the model (e.g. gastric secretion in the DGM). The pH is often monitored in real-time within dynamic models and is used to control the rate of addition of hydrochloric acid, allowing the acidification of the meal within the gastric compartment to follow a pre-determined curve. In dynamic models which incorporate a duodenal step, at this stage the pH of the chyme is neutralized by controlled addition of sodium bicarbonate solution, and secretions of bile and pancreatic enzymes (or pancreatin) are added.

Whilst the concentrations of enzymes, bile, electrolytes and phospholipids are set for the various secretions used in dynamic models, the concentrations of these components within the digesta cannot be readily determined. This is in part due to the dynamic nature of the models, allowing secretion rates to change throughout the digestion process. However, it is also due to the inhomogeneity of the bolus within

the models. In vivo, a solid meal will be ingested over a period of time as small balls of chewed food. Within the fundus of the stomach, the bolus is only subjected to gentle contractions and therefore is not well mixed. Whilst the outside of the bolus is acted upon by gastric secretions, it can take over 1 h for these secretions to penetrate to the center of the bolus (Marciani et al. 2001b). In the antral part of the stomach, strong peristaltic waves mix the bolus more readily, producing a more homogeneous chyme.

Some of the more advanced dynamic digestion models have a geometry designed to represent the fundus and antrum of the stomach, and/or the duodenum. These designs allow for the simulation of the physical forces exerted on the digesta during transit through the GI tract, which in turn allows for simulation of the inhomogeneous nature of digesta and localized biochemical environments, as in vivo.

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