

Chapter 7

Human Gastric Simulator (Riddet Model)

Maria J. Ferrua and R. Paul Singh

Abstract An in vitro ‘dynamic’ model for food digestion diagnosis, the Human Gastric Simulator (HGS), has been designed to reproduce the fluid mechanical conditions driving the disintegration and mixing of gastric contents during digestion. The HGS simulates the stomach as a flexible compartment, and mimics its contractive motility by a series of rollers that continuously impinge and compress the compartment wall with increasing amplitude. Operated at 37 °C, the HGS facilitates a precise control of the mechanical forces to which foods are exposed during the process, as well as of the rate of simulated gastric secretions and emptying patterns.

Applications of the HGS have illustrated the need to better understand, and mimic, the fluid mechanic conditions that develop during digestion to improve the performance and reliability of novel in vitro models. To date, the HGS has been used to analyse the digestion behaviour of different foods, and the role of their materials properties on the physicochemical changes that they experience during the process. While the ability of the HGS to reproduce the gastric forces that develop in vivo has been proved, further studies are needed to achieve a thorough validation of its digestive capabilities.

Keywords Human gastric simulator • In vitro model • Digestion • Gastric motility • Digesta fluid mechanics

7.1 Origins of the HGS

Central to the delivery of optimal nutrition, the stomach is, after the mouth, the main site for food disintegration during digestion (Wickham et al. 2012). Once in the stomach, products are stored, digested and progressively emptied into the

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duodenum by a synergy of physicochemical processes triggered and regulated by the motor and secretory activities of the gastric wall (Barrett and Raybould 2010a; Mayer 1994).

From a functional point of view, the stomach is divided into two main regions. Within the proximal region (upper half), changes in the compliance and secretory activity of the gastric wall allow the stomach to accommodate the ingested meal and provide the biochemical environment needed for its conditioning (Schwizer et al. 2002; Wickham et al. 2012). The distal region, on the other hand, is expected to play a major role in the structural disintegration of the meal. It is within this region where a series of peristaltic antral contraction waves (ACWs) continuously mix, compress and shear gastric contents during the process (Schwizer et al. 2006; Schulze 2006). As a result, food is converted into a semi-liquid mass of partially digested food, whose emptying from the stomach is feedback-regulated by a series of physicochemical receptors within the intestine (Barrett and Raybould 2010b).

Despite the complexities of gastric processes, increasing evidence indicates that the hydrodynamic conditions that develop during digestion have a central role on the material response and subsequent bioavailability of nutrients and bioactive compounds (Dikeman et al. 2006; Lentle and Janssen 2010). In particular, the poor *in vitro*–*in vivo* performance of many of the *in vitro* models currently used for digestion diagnosis has been largely attributed to their inability to reproduce the *in vivo* mechanics of the gastrointestinal (GI) tract (Yoo and Chen 2006).

Significant efforts have been made during the last decade to better understand the overall functioning of the human stomach and to develop a new generation of *in vitro* models of enhanced biochemical and mechanical relevance (Boulby et al. 1999; Faas et al. 2002; Kunz et al. 2005; Goetze et al. 2007, 2009; Kwiatek et al. 2006; Marciani et al. 2001a, 2007, 2012; Marciani 2011; Schwizer et al. 2002, 2006; Steingoetter et al. 2005; Treier et al. 2006; Mackie et al. 2013). More notably among those models are the TNO and DGM systems discussed in the previous sections. However, it is noteworthy that there is still no consensus agreement on the way in which these models reproduce the hydrodynamic conditions that develop *in vivo*, with none of them being able to replicate the actual motility of the gastric wall during digestion.

The Human Gastric Simulator (HGS) was specifically designed and developed by Kong and Singh (2010) to mimic the peristaltic activity of ACWs as reported *in vivo* (Kwiatek et al. 2006; Schwizer et al. 2006). Aimed at reproducing one of the main features driving the dynamics of gastric contents, this model is expected to better simulate the fluid mechanical forces driving food disintegration during digestion. Since its development, the HGS has been used to investigate not only the physicochemical changes experienced by different food products during digestion, but also the role of gastric motility on the outcomes of the process.

7.2 Model Description

The HGS consists of a cylindrical latex chamber that simulates the stomach compartment, and four conveyor belts that periodically impinge a series of Teflon rollers upon its wall to mimic the antral contraction wave activity of the stomach wall (Fig. 7.1). The system operates inside an insulated chamber maintained at 37 °C, while facilitating the delivery of gastric juices and emptying of simulated digesta in a continuous and controlled manner.

7.2.1 Gastric Compartment

The stomach is represented by a 5.7 L cylindrical vessel (20 cm high and 10.2 cm diameter) that ends in the form of a conic frustum (13 cm height and 2.5 cm final diameter).

Made of latex rubber, the gastric compartment sits straight up, wrapped onto a stainless steel ring (10.2 cm high and 15.2 cm diameter) that is supported by four

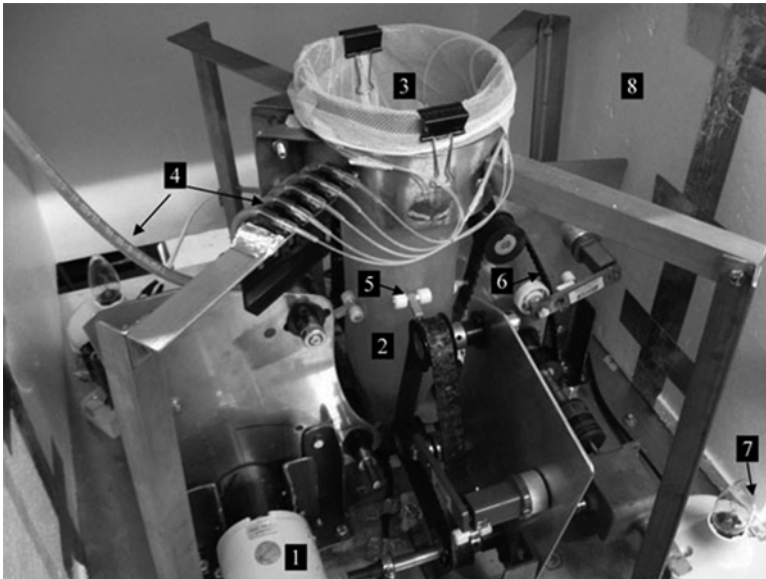


Fig. 7.1 Human gastric simulator. (1) Motor (2) Gastric compartment (3) Mesh bag (4) Simulating secretion tubes (5) Teflon roller set (6) Conveying belt (7) Insulated chamber. From Kong and Singh (2010)

diametrically opposed legs welded to the base. The open end of the container provides a simple way for loading food materials into the unit and for sampling of the simulated digesta during the process.

7.2.2 Gastric Motility

With the primary goal of mimicking the physical processes driving food disintegration, the HGS was designed to reproduce the motor activity of the antral contraction waves (ACWs) along the distal region of the stomach.

The dynamics of the ACWs along the lower part of the cylindrical vessel is mimicked by a mechanical drive system. Four conveyor rubber belts move along the height of the gastric compartment at 90° from each other.

Each belt is supported by four 0.95 cm pulleys, which attached to a low-carbon steel plate are moved by a drive shaft (1.27 cm diameter brass rod) connected to a 115 V Stir-Pak Heavy-Duty Mixer head (model R-50002-10, Cole-Parmer) motor. A Stir-Pak controller (model R-50002-02, Cole-Parmer) is used to allow for speed adjustments within the range of 2–180 rpm. Power is transmitted from one drive shaft to another via two bevel gears coupled at a 90° angle.

Each timing belt (0.95 cm wide) carries three sets of equally spaced Teflon rollers located every 20 cm of each other. Each set of rollers consists of two wide Teflon wheels (1.27 cm diameter, 0.9 mm long) placed together through an aluminium rod, that is secured to the belt by a male threaded screw (0.2 cm diameter, 1.5 cm long). As the belt moves, rollers start impinging the compartment wall (at about two-thirds of its total height). As the rollers propagate down, they replicate the increasing compression pattern of the ACWs by getting successively closer to the rollers on the opposite belt. The closer the rollers, the higher the compression forces.

To avoid possible interference between neighbouring rollers as they get further down the bottom of the gastric compartment, the lower pulleys closer to the compartment are placed at two different levels, with one pair of opposite pulleys located 3.0 cm higher than the other pair.

In order to simulate the motility pattern of the ACWs, the drive system is set to impose three propagating contractions per minute (with one finishing while another commences). If desired, this propagation speed can be changed by simply adjusting the rpm of the driving shaft. The force imposed by the rollers on the simulated digesta can be controlled by adjusting the distance between opposite rollers through the screw engagement depth inside the aluminium rod.

7.2.3 Gastric Emptying

To simulate the sieving effect of the pylorus, a polyester mesh bag (pore size of 1.5 mm) is used to line the inner surface of the gastric compartment and prevent larger particles from emptying the compartment. At the end of the trial, the mesh

can be easily taken out through the open top section of the compartment, facilitating the removal and analysis of the remaining digesta.

The rate of gastric emptying is controlled by means of a peristaltic pump (Masterflex Pump Controller 7553-50/7090-42 Pump, Cole-Parmer, Chicago, Ill., U.S.A.) connected to the bottom of the gastric compartment through a 0.32 cm plastic tube.

7.2.4 Gastric Secretions

Simulated gastric juices are delivered at about 10–15 cm from the bottom of the compartment through five polyethylene tubes (I.D. 0.86 mm) uniformly distributed between the mesh bag and the latex wall.

The delivery rate of the simulated gastric juice into the compartment is controlled by a mini peristaltic pump (Model 3385, VWR, Scientific, Rochester, N.Y., U.S.A.) and a control valve placed on a 6.4 mm plastic tube that later on divides into five tubes going into the compartment. The flow rate of the simulated secretion can be adjusted between 0.03 and 8.2 mL/min.

It is noteworthy that while it is possible to control the release of gastric juices during the simulated processes, there are no mechanisms in place to automatically adjust this gastric response to the specific composition and volume of simulated digesta.

7.2.5 Temperature Control

The system is placed inside an insulated plastic foam chamber, where two 60 W light bulbs and a mini-fan are installed to maintain the system operating at uniform and constant temperature of 37 °C. The operation of the bulbs is automatically controlled by a thermostat (Model T675A 1516, Honeywell, Honeywell Inc., Minneapolis, Minn., U.S.A.).

7.3 Analysis of HGS Biomechanical Relevance

The ability of the HGS to replicate the biomechanics of the human stomach was confirmed by analysing its ability to simulate the mechanical forces that develop in vivo (Kong and Singh, 2010). Based on the significant variation that exists on the levels of gastric forces and contractive activity of the stomach wall during digestion, the mechanical forces within the HGS were investigated for two different compressions levels: 50 % and 70 % (as determined by a minimum distance between opposite rollers of 1.2 cm and 0.6 cm, respectively). The HGS was filled with water and the forces that develop at the bottom of the compartment were determined by

measuring the pressure to which a rubber bulb is exposed due to the contractive activity of the rollers. Details of the experimental methodology and force computations can be found in Kong and Singh (2010). Normalized by the cross-sectional area of the bulb, the maximum stresses recorded within the HGS were 6.7 ± 1.2 kPa and 8.9 ± 2.5 kPa, for a 50 % and a 70 % of compression, respectively. As stated by the authors, these results, as well as the periodic changes in the pressure values inside the HGS, were in reasonably good agreement with in vivo data, that commonly report mechanical stresses varying from 5.1 to 67 kPa (Marciani et al. 2001b; Kamba et al. 2000).

7.4 Operating Protocol

To provide a reference frame for the operation of the HGS, a brief description of the methodologies applied during the use of the HGS is presented in the following.

7.4.1 *Preparation of a Food Bolus*

Different methods can be used to prepare the simulated bolus. In particular, during current applications of the HGS, food samples are either cut or ground to emulate the particle size distribution observed in human boluses. The particulate sample is then mixed with simulated saliva (100 g food: 20 mL saliva) for 30 s and allowed to stand at 37 °C for 2 min. The exact composition of the artificial saliva can be varied depending on the type of food and scope of the study (Kong and Singh 2010; Guo et al. 2014).

7.4.2 *Gastric Processing*

Simulated gastric juice is prepared by dissolving pepsin (1 g), gastric mucin (1.5 g), and NaCl (8.775 g) in 1 L distilled water with pH of 1.3 adjusted using 6 N HCl. To simulate the fasting conditions of the stomach, 50–70 mL of simulated gastric juice is first loaded into the HGS and equilibrated at 37 °C. The release of gastric juice within the gastric compartment starts immediately after the bolus is loaded, and continues at a rate of 2.5 mL/min during the entire processes (Hoebler et al. 2002). Gastric digesta is removed at a rate of 3 mL/min and subject to different chemical and physical analysis. Depending on study, after 3–5 h of simulated process the digesta remaining inside the HGS is removed for further analysis.

7.5 Uses of the HGS

The HGS has been used to investigate the role that ACW dynamics and food material properties have on the structural changes and disintegration profile of different foods during digestion.

7.5.1 *Role of ACW Activity on Food Digestion*

To investigate the relevance of ACW motility on the digestion behaviour of foods, Kong and Singh (2010) compared the performance of the HGS against the more traditional shaking bath method.

Apple cubes and extra-long white rice kernels were mixed with simulated saliva and exposed to 2 h of digestion in both, the HGS and a shaking bath. It is noteworthy that a batch approach was employed in both cases, with gastric juices being added to the systems only at the beginning of the process. The results clearly illustrated the significant effect that the crushing and squeezing forces generated within the HGS have on the breakdown of both food models during the process. In the case of the apples, 61 % of the total dry matter from the shaking bath was still in particles larger than 6.3 mm, and only 20 % in particles smaller than 2.8 mm. In comparison, only 16 % of the total dry matter from the HGS remained in particles larger than 6.3 mm, with a 69 % of it distributed in particles smaller than 2.8 mm. A similar result was found in the case of rice. Most kernels were intact after digestion in the shaking bath, while 52 % of the dry matter from the HGS was associated with particles smaller 0.8 mm.

Considering that the structural breakdown of the diet will have a significant impact on the rate of nutrient release during digestion, this study confirmed the need to better emulate the fluid mechanical conditions that develop during digestion. To further investigate the role of gastric motility on the disintegration kinetics of foods, Kong and Singh (2010) investigated the disintegration profile of white rice when exposed to two different levels of compression. Unlike the previous study, the HGS was operated under dynamic conditions, where a continuous release of 2.5 mL/min of gastric juice was imposed. In agreement with *in vivo* data, an exponential decay of the digesta's pH from an initial value of 4.27 to a final constant value of 1.35 was observed within the first 2 h of process. Simulated digesta was continuously removed from the HGS at a rate of 3 mL/min, leading to a 60 % of the total dry mass being emptied after 3 h of process. The HGS was operated under two levels of compression (50 % and 70 %). The higher the compression, the higher the disintegration of the food particles. In particular, a 75 % compression was able to break down 75 % of the rice kernels into particles much smaller than 1.2 mm in size. This study showed once again the need to better understand and mimic the biomechanical functions of the human stomach in order to improve the performance and reliability of *in vitro* digestive systems.

7.5.2 *Role of Food Material Properties*

Kong et al. (2011) used the HGS to investigate the physical changes that white and brown rice experience during digestion. The authors cooked the rice, mixed it with simulated saliva, and placed it in the HGS (previously loaded with 50 mL of simulated gastric juice). During the 3 h of process, gastric juice was added to the system at a rate of 2.5 mL/min. The simulated digesta was emptied at a rate of 3 mL/min and exposed to a maximum compression level of 50 %. The solid composition of the emptied digesta clearly illustrated the greater level of disintegration and dissolution experienced by white rice. After 3 h of digestion, 55 % of the white rice solids were emptied from the HGS, as compared with 45 % for the brown rice. Sieving of the digesta allowed the authors to associate the slower emptying rate of brown kernels to its slower rate of disintegration. By the end of the process, 80 % of the particles within the white rice digesta were smaller than 10 μm^2 compared to only 40 % for the brown rice. The differences observed in the physical changes of both types of rice were largely associated with the bran layer surrounding the brown kernels. As illustrated by the authors, this bran layer not only delayed the diffusion of gastric juice into the kernels, but also protected them from the mechanical forces that develop during the process. In addition, while both digesta samples behave as weak-gels, the brown rice digesta was found to have an enhanced elastic component, which could further slow down its mechanical disintegration.

Guo et al. (2014) used the HGS to investigate the effect of different emulsion gels' structures on their disintegration profile during digestion. Homogeneous 'soft' gels and heterogeneous 'hard' gels were mechanically grounded and mixed with artificial saliva to specifically simulate in vivo masticated gel boluses. The simulated boluses were loaded into the HGS already containing 70 mL of simulated gastric juice and exposed to 5 h of digestion process. Gastric juice was delivered at 2.5 mL/min and digesta samples removed at a rate of 3 mL/min (starting after 30 min). Rollers were set to impose a maximum compression level of 60 %. Despite the differences in the initial strength and size of the gel particles, similar amounts of solids were emptied from the HGS (≈ 74 %) at the end of the process, and a similar distribution of particles sizes was found in the digesta remaining inside the HGS. Despite this similarities, the authors did find significant differences in the emptying profile and size distribution of the digesta leaving the HGS during the process. Initially, the amount of solids leaving the HGS was higher in the case of the 'hard' gel, but this trend reversed after 3 h of process. This initial trend was explained by the smaller size of hard gel particles in the simulated masticated bolus. In addition, they also found that while the diameter ($d_{4,3}$) of oil droplets in the emptied digesta of the 'hard' gel did not change during the process, in the case of the soft gel it remained unchanged only for the first hour. After that time, the $d_{4,3}$ of emptied oil droplets from the 'soft' gel increased to reach a maximum at about 2.5 hours of process. These differences in the emptying profile of solids and size distribution of oil droplets at later stages of the process were related to the way in which the structure of gels influences their chemical digestion by pepsin. Within the first hour of

process, a combination of chemical and mechanical effects gradually broke down both gels to particles of about 10 μm . During this process, the microstructure of the gels was largely maintained and only very small quantities of oil were released. As time evolves, the fine-stranded structure of the 'soft' gel allowed pepsin to further disintegrate the gel particles down to a size of 0.45 μm (a process not observed in the case of the 'hard' gel). This further disintegration of the 'soft' gel enhanced its rate of emptying from the HGS and the release of oil droplets from the matrix. The transitional increase in the size of the liberated oil droplets after 1 h of process was associated with their flocculation, as the digesta passes through the isoelectric point of the denatured whey proteins.

7.6 Advantages and Limitations

Specifically designed to mimic the motor activity of the antral contractions waves during digestion, the HGS has been proved to reproduce the fluid mechanical forces that develop *in vivo*. Preliminary applications of the HGS have demonstrated the need to better understand and mimic the physical processes underlying digestion. The possibility to control the motor activity of the ACW offer new opportunities to investigate the impact gastric motility dysfunctions on food digestion. Further efforts needs to be done to automate the secretory and emptying patterns of the HGS in response to digesta properties during the process, and to pursue a thorough validation of its digestive capabilities.

7.7 Availability of the System

Two HGS models are in operation. One in the Department of Biological and Agricultural engineering at the University of California (Davis), where it was first created. A second replicate was made and currently used at the Riddet Institute, Massey University (New Zealand).

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