Chapter 6
Dynamic Gastric Model (DGM)

Eva C. Thuenemann, Giuseppina Mandalari, Gillian T. Rich, and Richard M. Faulks

Abstract The Dynamic Gastric Model (DGM) was developed at the Institute of Food Research (Norwich, UK) to address the need for an in vitro model which could simulate both the biochemical and mechanical aspects of gastric digestion in a realistic time-dependent manner. As in the human stomach, masticated material is processed in functionally distinct zones: Within the fundus/main body of the DGM, gastric acid and enzyme secretions are introduced around the outside of the food bolus which is subjected to gentle, rhythmic massaging. Secretion rates adapt dynamically to the changing conditions within this compartment (acidification, fill state). Portions of gastric contents are then moved into the DGM antrum where they are subjected to physiological shear and grinding forces before ejection from the machine (and subsequent separate duodenal processing).

The DGM has been used extensively for both food and pharmaceutical applications, to study, for example, release and bioaccessiblity of nutrients and drugs. The system allows the use of complex food matrices (as used in in vivo studies) and processes these under physiological conditions in real-time, thereby providing a realistic tool for the simulation of human gastric digestion.

Keywords Dynamic gastric model • Physiological • Gastric • In vitro • Digestion • Bioaccessiblity • Nutrient • Dissolution • Pharmaceutical • Real-time

6.1 Origins and Design of the DGM

The Dynamic Gastric Model was developed at the Institute of Food Research (Norwich, UK) to address the need for an in vitro model which could simulate both the biochemical and mechanical aspects of human gastric digestion in a realistic

E.C. Thuenemann (✉)
John Innes Centre, Colney Lane, Norwich, Norfolk NR4 7UH, UK
e-mail: eva.thuenemann@jic.ac.uk

G. Mandalari • G.T. Rich • R.M. Faulks
The Model Gut, Institute of Food Research, Norwich Research Park, Colney Lane, NR4 7UA Norwich, UK

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time-dependent manner. This was initially done in the interest of food-based research to enable the study of parameters such as nutrient bioaccessibility, effect of food structure on nutrient delivery, nutrient interactions, survival and delivery of functional foods. Over the years, the DGM has also increasingly been used by pharmaceutical industry as an in vitro tool to study the effect of food matrices on the disintegration and dissolution of drug formulations and delivery profile to the duodenum. This is in part due to its ability to realistically process any complex food matrix for direct comparison with the results of in vivo/clinical studies.

The design of the DGM is based on extensive research into the process of digestion and the physiology of the human stomach, both biochemical and mechanical (reviewed by Wickham et al. 2012). It builds on these findings as well as literature data to closely mimic the conditions encountered by food particles and drug formulations as they move through the upper gastrointestinal tract. To this end, digestions using the DGM are performed in real-time, and the length of each experiment is designed around the estimated gastric residence time of the particular meal used. Experiments typically last between 25 min (glass of water) and 4.5 h (high-fat FDA breakfast) depending on meal size, composition and calorific content.

The following paragraphs provide an introduction to the parts of the DGM and how these are used to simulate the natural physiology of the healthy adult human stomach (from ingestion to release into the duodenum). Schematic drawings and further descriptions are provided in Fig. 6.1 and Table 6.1 respectively.

Masticated food, a complex inhomogeneous mixture of accessible and inaccessible protein, carbohydrate and fat (in particles of varying sizes) as well as water and saliva, enters the stomach in portions from the esophagus. It initially encounters an acidic environment of resting gastric fluid (24±5 ml, Dubois et al. 1977), whose pH is subsequently altered by the buffering capacity of the meal. In the DGM, masticated food can be introduced in real-time or as a bulk from the top into the fundus and main body (Fig. 6.1), where it encounters a previously added 20 ml volume of gastric priming acid (Table 6.2).

Initiation of gastric digestion of a food bolus in the stomach is via secretions from the mucosal gastric surface and a change from resting to rhythmic phase 2 contractions. The secretion rates of acid and enzyme are dependent on, amongst others, the composition of the food bolus and fill volume of the stomach, and are therefore not constant throughout the digestion process but change in response to factors such as the acidification of the bolus and emptying of the stomach contents into the duodenum (Konturek et al. 1974; Schubert and Peura 2008). Within the DGM, gastric acid and enzyme solutions (Table 6.2) are added through a perforated hoop situated around the wall of the fundus (Fig. 6.1 and Table 6.1). The flow rates of these secretions is controlled dynamically: The rate of gastric acid addition slows gradually in response to the acidification of the meal as detected by the pH electrode inserted within the fundus; The rate of gastric enzyme addition slows in response to the gradual decrease in food bolus volume as recorded in response to ejection of samples from the antrum.

The human stomach has distinct zones which differ markedly in the physical forces applied to the meal bolus: the fundus/main body (proximal) and the antrum

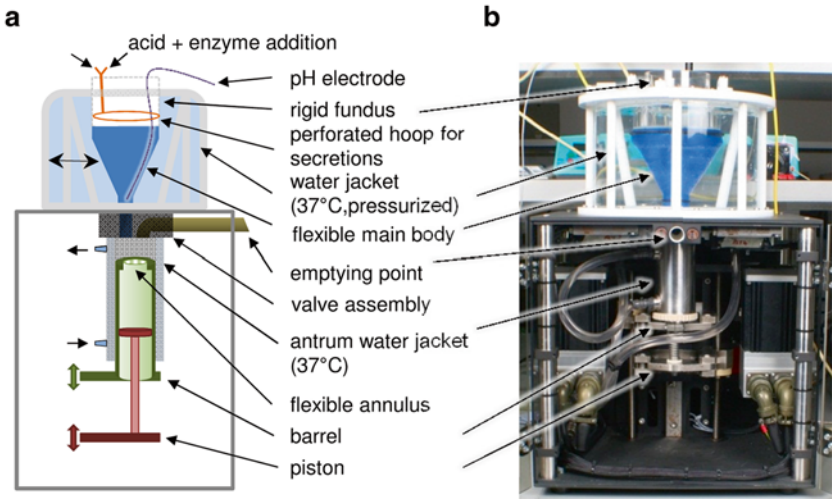
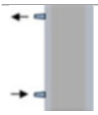


Fig. 6.1 The dynamic gastric model (DGM). (**a**) Schematic representation of the main components of the DGM (*side view*) (**b**) Photographic image of the DGM (*front view*)

(distal) (Bornhorst and Singh 2014). Within the fundus, the meal is subjected to low physical forces exerted by gentle rhythmic peristaltic contractions. Upon ingestion, the bulk of the meal resides within this part of the stomach and it was found that the penetration of this bolus by acidic gastric secretions occurs very slowly (Marciani et al. 2001b). Additionally, it has been shown that gastric secretions can form an acidic pool on top of a dense meal (Holloway and Sifrim 2008). This not only influences conditions such as gastric reflux disease, but also has a bearing on the microenvironment encountered by drug formulations when they are taken after a meal. The DGM also models the two distinct regions of the stomach. Within the fundus/main body, the food bolus is subjected to rhythmic squeezing brought about by cyclical pressurization of the 37 °C water jacket surrounding the main body. Depending on the meal viscosity, the gastric secretions applied to the outside surface of the fundus can take a considerable amount of time to fully acidify the meal bolus. Also, a pool of gastric secretions forms on the surface, mimicking the phase separation of the meal within the stomach.

Within the antral part of the human stomach, the food bolus is subjected to higher shear forces and turbulence, resulting in greater mixing as well as gradual size reduction of particles. Peristaltic contractions push the food towards the pyloric sphincter which provides resistance resulting in retrograde movement of the chyme which is pushed forwards again by the next contraction (Ferrua and Singh 2010). Within a meal of high viscosity, the shear and grinding forces are higher than in a meal of low viscosity, as shown in an in vivo study of the gastric residence time of agar beads of different strengths within the two meal types (Marciani et al. 2001a). A similar study using the same agar beads and meal types was conducted in the DGM to calibrate the physical forces within the DGM antrum

Table 6.1 Functional parts of the DGM

Schematic[a]	Name[a]	Functions	Relevance in vivo
	pH electrode	Records pH within DGM main body, enabling automatic adjustments to gastric acid flow rate (within physiological production rates) in response to acidification of meal. Can be forced outside of "normal" range if necessary	Gastric acid production is controlled through a pH-regulated feedback loop
	Perforated ring for gastric secretions	Distribution of gastric secretions around outside of DGM main body, fed by computer-controlled pumps. Secretion rates respond dynamically to pH and volume changes of food bolus	Acid and enzymes are secreted from the walls of the stomach and can form an acid pool on top of the meal
	Water jacket	Maintains DGM main body at 37 °C allowing heat transfer to food bolus. Enables gentle mixing within DGM main body by cyclical pressurization	Normal body temperature is ca. 37 °C
	Rigid fundus and flexible main body	Holds up to 800 ml of masticated real food and drink. Gentle mixing due to cyclical pressurization of water jacket. Heat transfer rates from 37 °C water jacket similar to those in vivo	Typical meal sizes are less than 1 l Main body of stomach is characterized by gentle movements and slow mixing
	Valve assembly	Inlet valve allows movement of portions of food bolus from main body into antral part of DGM. Inlet valve allows retrograde movement from antral part to main body during processing outlet valve allows ejection of samples from DGM	Phase II contractions periodically empty digesta from antrum through pyloric sphincter into the duodenum
	Antrum water jacket	Maintains antral temperature at 37 °C	Normal body temperature is ca. 37 °C
	Barrel and flexible membrane	Barrel moves flexible membrane rhythmically through food bolus contained within antral part of DGM, creating an environment of high shear and mixing	Contractions of the proximal stomach strengthen towards the antrum, creating potentially high shear forces dependent on meal viscosity and particle sizes
	Piston	Allows food bolus to move from main body through valves into antral part of DGM Compensates volume changes within antrum due to barrel movement to modulate reflux Maintains a dead volume within barrel to simulate gastric sieving	Large, dense food particles and/or pharmaceuticals can sink to the greater curvature of the stomach, thereby delaying their emptying from the stomach (gastric sieving)

The main functions of each part along with their relevance to the human stomach are given
[a]Schematic representations and names of parts refer to Fig. 6.1

Table 6.2 Composition of solutions used in the DGM

Solution	Component	Source	Concentration[a]
Artificial saliva (pH 6.9)	Salt (NaCl)	Sigma[b]	150 mM
	Urea	Sigma[b]	3 mM
	Salivary amylase (human)	Sigma[b]	36 U/ml
Gastric priming acid	Salts (NaCl, KCl, $CaCl_2$, NaH_2PO_4)	Sigma[b]	89 mM (total)
	HCl	Sigma[b]	10 mM
Gastric acid	Salts (NaCl, KCl, $CaCl_2$, NaH_2PO_4)	Sigma[b]	89 mM (total)
	HCl	Sigma[b]	200 mM
Gastric enzyme	Salts (NaCl, KCl, $CaCl_2$, NaH_2PO_4)	Sigma[b]	89 mM (total)
	Egg lecithin	Lipid P.[c]	0.38 mM
	Lipase (fungal, DF15)	Amano[d]	60 U/ml
	Gastric pepsin (porcine)	Sigma[b]	8.9 kU/ml
Duodenal hepatic	Salts (NaCl, KCl, $CaCl_2$)	Sigma[b]	154 mM (total)
	Egg lecithin	Lipid P.[c]	6.5 mM
	Cholesterol	Sigma[b]	3 mM
	Bile salts (Na-taurocholate, Na-glycodeoxycholate)	Sigma[b]	25 mM (total)
Duodenal pancreatic	Salts (NaCl, KCl, $CaCl_2$, $MgCl_2$, $ZnSO_4$)	Sigma[b]	154 mM (total)
	Pancreatic lipase (porcine, Type VI-S)	Sigma[b]	590 U/ml
	Colipase (porcine)	Roche[e]	0.2 mg/ml
	Trypsin (porcine, Type IX-S)	Sigma[b]	11 U/ml
	α-Chymotrypsin (bovine, Type II)	Sigma[b]	24 U/ml
	α-Amylase (porcine, Type VI-B)	Sigma[b]	300 U/ml

[a]Stated concentrations are within the stock solutions used. Final concentrations within gastric/duodenal compartment will be significantly lower due to dilution with food bolus and other solutions, bringing them within physiological ranges presented in literature
[b]Sigma Aldrich, Gillingham, Dorset, UK
[c]Lipid Products Ltd, Redhill, UK
[d]Amano Enzyme Inc., Nagoya, Japan
[e]Roche Diagnostics GmbH, Mannheim, Germany

(Vardakou et al. 2011a). The two studies show a good correlation between the physical forces of the human stomach and the DGM antrum, using both low viscosity and high viscosity meals.

The DGM antrum consists of a barrel and a piston, which move within a 37 °C water jacket (Fig. 6.1). While the piston draws portions of food bolus through an inlet valve from the fundus into the antrum, it is the upward and downward movement of the barrel during processing which exerts shear stresses on the antral contents. This is due to a flexible annulus mounted within the top part of the barrel through which food (and formulations) passes during every stroke, thereby simulating the rhythmic peristaltic contractions of the human stomach. While the speed of movements has been calibrated to provide physiological shear forces (Vardakou et al. 2011a), the actual volume of food bolus processed within the antrum at any one time, as well as duration of processing are tailored to the specific meal used (volume, composition,

calorific content). At pre-defined intervals, the inlet valve closes and the outlet valve opens, allowing the processed chyme to be ejected from the DGM.

A phenomenon observed in the human stomach is that of gastric sieving, whereby larger, denser particles/formulations can be retained within the greater curvature of the stomach longer than smaller particles, therefore subjecting them to extended processing (Meyer 1980). Gastric sieving is simulated within the DGM by definition of a "dead volume," i.e. a defined space between barrel and piston whose volume is maintained during ejection thereby allowing large, dense particles to remain in the antrum and undergo repeated processing cycles. At the end of a simulated digestion, any material remaining in this dead volume is ejected to simulate the phase III contraction (housekeeper wave) which fully empties the human stomach at the end of gastric digestion (Meyer 1987).

Following ejection from the DGM, samples can be subjected to further digestion using a static duodenal model. To this end, the pH of the samples is elevated and a physiological mix of bile salts with lecithin and cholesterol and pancreatic enzymes, is added to simulate conditions found within the duodenum.

6.2 General Protocol for DGM Experiments

Planning First, the following information about the test meal (and/or drink) is gathered: mass, energy content, composition (carbohydrate, fat, protein content). This information is used to estimate total gastric residence time of the meal as well as maximum rate of gastric secretion.

Using parameters such as the volume and frequency of ejection from the antrum, a program is designed to allow the DGM to empty the test meal fully within the calculated gastric residence time. The chosen sample volume and frequency are dictated by the gastric residence time and volume of the meal, as well as any downstream processing and analysis of the samples which may require certain minimum volumes to be ejected.

Preparation Any enzyme solutions needed during the experiment (salivary, gastric, duodenal) are prepared immediately prior to the experiment. The components of solutions and enzymes used in the experiments are detailed in Table 6.2. Solutions have been designed to provide biochemical conditions (e.g. concentrations of salts, enzymes, etc., and/or secretion rates) within the "normal" physiological range of healthy subjects (Lentner 1981). For example, the contents of the DGM at any one time will be a complex inhomogeneous mixture of food matrix and the components of gastric priming acid, gastric acid and gastric enzyme solutions.

Mastication Depending on the requirements of the project and food type, several methods of mastication can be used.

- No mastication (e.g. for liquid meals, drinks and meals where mastication is not required)
- Simulated mastication using a food processor, mincer or grinder, with or without addition of artificial or human saliva

- Human chew, whereby the test meal is chewed to the naturally perceived point of swallowing and collected in a beaker before addition to the DGM
- Real-time human chew, similar to the above but with real-time transfer of each mouthful to the DGM

Dynamic Gastric Processing Before the start of gastric processing, the DGM pH electrode is allowed to equilibrate in the test meal/drink. This sets the range of pH during processing of this specific meal (from start reading to pH 2) and allows the DGM to dynamically adjust gastric acid addition as the pH drops. The DGM is primed with 20 ml priming acid to simulate the residual gastric fluid normally found in the resting human stomach.

Upon start of the program, the meal is added to the fundus of the DGM. Fluid portions of the meal are poured slow over a spoon and allowed to trickle down the outside edge of the fundus and main body. This simulates how fluid would enter the stomach from the esophagus and minimizes any artificial turbulence and mixing of the gastric contents. Masticated foods are usually added slowly over the course of several minutes to mimic the swallowing of food.

Any food/drink added at the start of a run is immediately in contact with the walls of the main body, allowing heat transfer to occur. The contents are also subjected to gentle squeezing in the main body (three contractions per minute). Gastric acid and enzyme secretions are added through the perforated ring at physiological rates dependent on meal size and buffering capacity. These rates slow down progressively during the experiment in response to reducing bolus volume and change in pH. Shortly after start of the run, the lower part of the DGM is activated and pulls a portion of the food bolus into the antrum for processing (high shear, mixing).

At programmed intervals, the inlet valve of the DGM closes, the outlet valve opens and the defined proportion of bolus from the antrum is ejected by an upward movement of the barrel and piston. Any pre-defined dead volumes between piston, barrel and valves are maintained to allow for large dense particles to remain in the machine for further processing (gastric sieving). The outlet valve then closes, the inlet valve opens and the next portion of partially digested food enters the antrum from the main body.

At the end of the DGM run, the final sample is ejected by complete upward movement of barrel and piston, thereby ejecting any remaining dead volumes that were present in the antrum region and simulating the housekeeper wave. The DGM is disassembled to recover any residues.

Static Duodenal Processing Where required, samples from the DGM can be subjected to further static digestion in a duodenal model. First, the pH of the sample is adjusted to pH 6.8 to reduce further activity of gastric enzymes and to simulate the change of pH in the duodenum. One of two main methods is then employed:

- From each DGM gastric sample, a subsample is transferred to a separate vessel, and pancreatic enzymes as well as bile salts, lecithin and cholesterol are added at physiological levels depending on food. These separate duodenal incubations (3–4 h each in an orbital shaker, 170 rpm, at 37 °C) can then be sampled at defined intervals to establish separate duodenal nutrient/pharmaceutical release

profiles for each gastric ejection. This approach is often followed for nutrient bioaccessibility studies and pharmaceutical studies using formulations that disperse in the stomach.
- Subsamples of each DGM gastric sample are neutralized and pooled in a single vessel and kept on ice until the end of the gastric phase. Pancreatic enzymes and bile salts, lecithin and cholesterol are added at physiological levels depending on food, and the vessel is incubated in an orbital shaker for 3–4 h at 170 rpm, 37 °C. Samples are taken at defined intervals to establish a single duodenal release profile. This method is often used for gastro-resistant pharmaceutical formulations which are recovered from the DGM intact and transferred to this duodenal pool to monitor dispersal and dissolution in the duodenal phase.

Controls Control experiments are designed for any project involving DGM runs. In the case of food applications such as bioavailability studies, these control runs essentially follow the same protocol as the actual experiments, but do not include any digestive enzymes. The starting material before gastric digestion is also analysed. This enables a distinction to be made between the effects of mechanical processing in the DGM alone, and full mechanical and biochemical digestion. For pharmaceutical applications, control experiments generally follow the full experimental protocol including enzymes but without the drug.

DGM experiments are generally carried out in triplicate in the first instance.

6.3 Uses of the DGM

The DGM has a wide variety of applications and has so far been used to study nutrient bioaccessibility and structural changes of food matrices during digestion, as well as the disintegration and dissolution of various drug formulations. Normal experimental readouts include a photographic/video record of digesta appearance, acidification profile and temperature profile. Some previously studied parameters are summarized Table 6.3.

6.3.1 Food-Based Research

The DGM has extensively been used to evaluate the rate and extent of nutrient and phytochemical release from plant foods and the effect of food matrix on their release in the upper GI tract (Mandalari et al. 2010, 2013). The effect of mastication and processing on the lipid release from almond seeds in the upper GI tract has recently been investigated (Mandalari et al. 2014a).

The bioaccessibility of pistachio polyphenols, xanthophylls and carotenoids during simulated human digestion was recently assessed using the DGM followed by duodenal incubation: results demonstrated that the presence of a food matrix, such as muffin, decreased the bioaccessibility of certain polyphenols in the upper GI tract (Mandalari et al. 2013).

Table 6.3 Applications of DGM samples (this list is not exhaustive)

Parameter	Method of analysis	Output	References
Viscosity	Rheological analysis	Plot of changes in viscosity	
Cellular structure	Microscopy	Changes in cell/surface integrity	Mandalari et al. (2014b)
Phytochemicals bioaccessibility	GC, HPLC	Effect of food matrix on the bioaccessibility of bioactives from pistachios during simulated digestion	Mandalari et al. (2013)
Starch digestion	Starch analysis	Changes in ratio of glucose:starch, total starch Effect of particle size on starch degradation from *Durum* wheat	Ballance et al. (2013) IFR, unpublished data
Lipid separation (digestion?)	Total lipid release and fatty acid analysis	Effect of mastication and processing on lipid release from almond seeds	Mandalari et al. (2014a)
Protein digestion	1D and 2D SDS-PAGE, RP-HPLC, MALDI-ToF, immunoblotting	Effect of food matrix on protein digestion from almond seeds	Mandalari et al. (2014b)
Peptide production	1D and 2D SDS-PAGE, RP-HPLC, MALDI-ToF, immunoblotting	Persistence of allergens from cow's milk and peanut flour	IFR, unpublished data
Probiotic survival	Culturing on selective media	Effect of food matrix on probiotic survival in the upper GI tract	Lo Curto et al. (2011) and Pitino et al. (2010, 2012)
Prebiotic delivery	Culturing on selective media, genetic analysis	Delivery of potential prebiotics in the distal GI tract	Mandalari et al. (2010)

Ongoing research aims to establish the key parameters involved in starch digestion from cereal (Ballance et al. 2013) and *Durum* wheat (IFR, unpublished data). The data obtained using the DGM compared well with in vivo data of glycaemic response, indicating that the DGM was predictive of the kinetics of digestible starch hydrolysis (Ballance et al. 2013).The effect of particle size on starch degradation from *Durum* wheat is currently being investigated using the DGM coupled with the static duodenal model and compared with an in vivo ileostomy study (IFR, unpublished data).

The DGM has recently been used to assess digestibility of almond protein in the upper GI tract, evaluate the effects of food matrix on protein release and assess the persistence of immunoreactive polypeptides generated during simulated digestion (Mandalari et al. 2014b). The results obtained are useful to investigate the relationship between food matrix and almond allergy.

The persistence of allergens present in cow's milk and peanut flour as measured by gastric and duodenal aspirates from human volunteers has been compared with data sets obtained from similar meals processed by the DGM. The comparison suggests that the DGM was predictive, not only of the persistence of the original allergens, but also of the profile of peptide fragments generated during digestion (IFR, unpublished data).

Probiotic strains of *Lactobacillus* spp. were investigated for their ability to survive in the upper GI tract using a number of vehicles and different growth phases: the results obtained showed that probiotic survival using dynamic models was affected by the buffering capacity of the matrix in relation to the pH decrease in the stomach (Lo Curto et al. 2011; Pitino et al. 2010). Cheese was also found to be a good vehicle for passage of probiotic bacteria in the upper GI tract and scanning electron microscopy indicated production of extracellular polysaccharides by *Lactobacillus rhamnosus* strains as a response to acid stress in the gastric compartment (Pitino et al. 2012).

A full model of the gastrointestinal tract, including in vitro gastric and duodenal digestion, followed by colonic fermentation using mixed faecal bacterial cultures, was used to investigate the prebiotic potential of natural (NS) and blanched (BS) almond skins, which are rich in dietary fiber (Mandalari et al. 2010). Both NS and BS significantly increased the population of bifidobacteria and *Clostridium coccoides*/*Eubacterium rectale* group, which are known for their beneficial effect in relation to health.

6.3.2 Pharmaceutical-Based Research

In recent years, the DGM group has seen a marked increase in projects from pharmaceutical industry. Current in vitro methods used in the study of disintegration and dissolution of oral solid dosage forms do not provide a physiological representation of the dynamic biochemical and physical environment of the human stomach (Vardakou et al. 2011a) and are therefore sometimes not predictive of the in vivo behaviour of dosage forms, particularly in the case of dosing with or after a typical meal. The DGM is well placed to bridge the gap between these simpler dissolution tests and in vivo studies (animal or human) and can be used in either to explain unexpected in vivo results, or as a predictive tool (Mann and Pygall 2012; Wickham et al. 2009).

Past studies in the DGM have involved a wide variety of dosage forms (capsule, tablet, powder, liquid) and types e.g. immediate release, modified release, gastro-retentive, self-emulsifying drug delivery system (Vardakou et al. 2011b; Mercuri et al. 2009, 2011). Particularly in the case of gastro-retentives, the ability to introduce sequential meal cycles (e.g. breakfast, lunch, dinner) within the same experiment allows for the real-time, realistic simulation of the range of conditions (pH, viscosity, shear forces) that these formulations are likely to encounter in vivo. The DGM may also find future use in the assessment of alcohol-drug interactions (dose-dumping) as well as the modelling of pediatric and/or geriatric physiology, all of which provide challenges (ethical and otherwise) in the justification of in vivo tests.

6.4 Advantages, Disadvantages and Limitations

Some advantages and limitations of the DGM are provided in (Table 6.4).

Table 6.4 Advantages and limitations of DGM

Advantages	Limitations
Capacity: Full meals up to 800 ml	*Not transparent*: Visual observations not possible during antral processing
Meals: Any masticated food/drink matrix	*Orientation*: Vertical alignment of main body and antrum
In vivo correlation: Use of exact meal used in a clinical study	*Open top*: Fundus always exposed to air
Temporal simulation: Real-time digestion and monitoring of pH and temperature	*Satiety*: no in vivo satiety signals controlling rate of digestion
Temporal simulation: allows time dependent processes to be studied	
Sequential meals: A full day's feeding regimen can be followed in real-time	

6.5 Availability of the System

At the time of writing, two DGM machines are in operations (Mark I and Mark II), with a third machine in development. The machines can be used for food- and pharmaceutical-based research, by both industry and academia. The Dynamic Gastric Model is protected by granted patents and pending patent applications owned by Plant Bioscience Limited (PBL). Enquiries about purchasing a DGM unit for academic or commercial use should be directed to PBL (Plant Bioscience Limited, Norwich, UK; martin@pbltechnology.com; http://pbltechnology.com). Access to the DGM as an outsourced contract research facility is available exclusively through Bioneer:FARMA (Bioneer:FARMA, Copenhagen, Denmark; bioneer@bioneer.dk; http://www.bioneer.dk/DGM/).

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