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Engineering Digestion: Multiscale Processes of Food Digestion

Gail M. Bornhorst, Ourania Gouseti, Martin S.J. Wickham, and Serafim Bakalis

Abstract: Food digestion is a complex, multiscale process that has recently become of interest to the food industry due to the developing links between food and health or disease. Food digestion can be studied by using either *in vitro* or *in vivo* models, each having certain advantages or disadvantages. The recent interest in food digestion has resulted in a large number of studies in this area, yet few have provided an in-depth, quantitative description of digestion processes. To provide a framework to develop these quantitative comparisons, a summary is given here between digestion processes and parallel unit operations in the food and chemical industry. Characterization parameters and phenomena are suggested for each step of digestion. In addition to the quantitative characterization of digestion processes, the multiscale aspect of digestion must also be considered. In both food systems and the gastrointestinal tract, multiple length scales are involved in food breakdown, mixing, absorption. These different length scales influence digestion processes independently as well as through interrelated mechanisms. To facilitate optimized development of functional food products, a multiscale, engineering approach may be taken to describe food digestion processes. A framework for this approach is described in this review, as well as examples that demonstrate the importance of process characterization as well as the multiple, interrelated length scales in the digestion process.

Keywords: food digestion, food engineering, *in vitro*, *in vivo*, multiscale, unit operations

Introduction

In many developed countries, a segment of the population exhibits malnutrition (having a low micronutrient intake) while simultaneously being overweight (having excess energy consumption). Additionally, the link between dietary patterns with health and disease has been strengthened. Specific food consumption patterns have been shown to increase or decrease risk for type II diabetes, cardiovascular disease, obesity, and certain cancers (Trichopoulou and others 1995; Levi and others 1998; Dahm and others 2010; Malik and others 2010; Sun and others 2010; Ye and others 2012). These links have driven increased consumer awareness to the functional properties of the foods they consume, and have prompted the food industry to develop innovative "functional food" products, or food products with functional ingredients. Functional food products may contain certain ingredients, such as antioxidants or dietary fiber, or they may have a certain structure or formulation in order to modify their functional properties after consumption (Hertog and others 1993; Benini and others 1995; McClements and others 2008).

To develop these innovative food products, it is necessary to understand the behavior of food during the digestion process, from its initial physical breakdown, to the transformation and absorption of its constituent nutrient molecules. Additionally, it is important to understand the digestive system parameters, such as secretion rates, contraction frequency, and contraction depth. With the recent advances in noninvasive measurement techniques, such as magnetic resonance imaging (MRI), our understanding of gastrointestinal physiology has increased. For example, multiple studies have used MRI to demonstrate that the muscular contraction frequency in the stomach is approximately 2 to 3 contractions per minute (Schwizer and others 1996; Kunz and others 1999; Marciani and others 2001a,c; Kwiatek and others 2006). Such information is necessary in order to design functional systems that mimic the gastrointestinal tract.

Although the complex, interrelated processes of food digestion may seem like an extremely challenging system, they can effectively be related to similar unit operations found in food or chemical plants, many of which are well-characterized. By taking an engineering approach to study food digestion, each individual physical and chemical process can be related to common unit operations. For example, crushing or grinding is a parallel unit operation to food breakdown during mastication, and membrane separation is a parallel unit operation to nutrient absorption in the small intestine (McCabe and others 2005). This approach will provide additional quantitative information which will allow for a more advanced description of food digestion processes.

The interest in simulating digestion to understand food behavior in the gastrointestinal tract is growing, as food digestion models may be used as tools in food product development. These tools can assist in predicting food behavior after ingestion *in vivo*, permitting better-informed food product design and useful interventions to improve consumer health.

This concise review is based on a session presented at the 2014 IFT Annual Meeting. The scope of this concise review includes a rationale and overview of food digestion, including different approaches used to study the digestion process, a description of the parallels between digestion processes and engineering unit operations, and case studies of the multiscale processes that occur during digestion of various food products.

Approaches to Study Food Digestion

The human gastrointestinal tract is a complex system that ranges from mouth to anus. It transforms ingested foods into nutrients that can be absorbed by the body to maintain the health of the

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consumer (Wickham and others 2009; Bornhorst and Singh 2014). The behavior of foods during digestion can be studied using *in vivo* (animal or human) or *in vitro* (laboratory) methods.

In vivo methods have been used to study many types of food products and nutrients. They provide direct data on nutrient bioavailability, which allows for determination of the amount of nutrient, bioactive compound, or other beneficial substance absorbed in human or animal subjects. For example, glucose response after consumption of carbohydrate-based food products has been widely studied (Jenkins and others 1988; Wolever and others 1991; Kendall and others 2011). To measure glucose response *in vivo*, blood samples are taken from a human subject at specific times before and after food consumption to determine the glucose response profile. Similar methods have also been used to study lipid, mineral, vitamin, or phytochemical absorption in human and animal models (Yeum and Russell 2002; Parada and Aguilera 2007; Cassady and others 2009).

The advantage of *in vivo* approaches is that results are directly applicable to human food consumption. However, variations between individuals may lead to large differences in responses, making data interpretation challenging. Additionally, most human *in vivo* studies focus on end-point measurements, without taking into account the individual breakdown and absorption processes that occur during digestion. Specific knowledge of food digestion mechanisms may be more useful than only end-point measurements, but are rarely obtained during *in vivo* studies due to sampling and ethical limitations. In addition, conducting *in vivo* trials is costly, resource demanding, and ethically controversial.

Consequently, *in vitro* testing is commonly conducted as a suitable alternative to *in vivo* experiments. *In vitro* testing allows for rapid screening of food formulations or ingredients with varying composition and structure as well as hypothesis development and mechanistic studies in a controlled environment (Hur and others 2011; Minekus and others 2014). Recently developed *in vitro* models have adopted an advanced approach to controlling and examining a wide variety of parameters, both physical and chemical, to adequately mimic the conditions in the gastrointestinal tract.

In vitro digestion models incorporate, at the minimum, the enzymatic and pH conditions found in the mouth, stomach, and intestines, with some models also including various types of mechanical and/or hydrodynamic forces. Using *in vitro* model systems, structural changes in foods during digestion, nutrient release, and nutrient digestibility can be studied in a controlled environment. *In vitro* digestion models have been used in food and nutritional science, environmental toxicology, and pharmacology. Examples of previous applications of *in vitro* models include: digestibility of food proteins, including allergens (Wickham and others 2009; Kaur and others 2010), bioaccessibility of phytochemicals (Alminger and others 2014), bioaccessibility of soil contaminants (Oomen and others 2003), and kinetics of food disintegration (Bornhorst and Singh 2013), among many other applications.

The advantages of using *in vitro* model systems include: lower cost, absence of ethical concerns, ability to screen large numbers of food products, and the ability to study the mechanisms of processes (as opposed to end-point measurements only). However, it is difficult to accurately simulate the complex physicochemical environment in the gastrointestinal tract. Determination of physiologically accurate values for model parameters, such as pH and enzyme concentration, is not straightforward, as values reported from *in vivo* studies show considerable variation between subjects (Ulleberg and others 2011). Additionally, specific times, pH, enzyme content and concentration, and presence of physical and/or hydrodynamic forces vary between each *in vitro* study, making results hard to compare across studies using dissimilar methodologies. Recently, a standardized *in vitro* testing method has been proposed (Minekus and others 2014), which may help to facilitate future comparison across studies. The absence of physical and/or hydrodynamic forces in many *in vitro* model systems may neglect some of the key aspects of structural breakdown, however these forces are more difficult to mimic in an *in vitro* model system. Although *in vitro* systems have challenges associated with developing a physiologically accurate and consistent methodology, they represent a cost-effective and ethical alternative to *in vivo* studies that can be used to study mechanisms of the food digestion process on a large-scale basis.

An additional consideration in the development and use of *in vitro* models is the need for *in vitro–in vivo* correlations to be able to link outputs from *in vitro* models to end-point measurements *in vivo* (Fatouros and Mullertz 2008). At this time, *in vitro* models are intended to be used as tools for initial product screening and development of a mechanistic understanding of the digestion process, and need to be complemented with *in vivo* studies. Currently, *in vivo* studies are the standard method for measuring nutrient bioaccessibility in target populations (Fernández-García and others 2009). Further development of *in vitro* and *in vivo* studies of food behavior during digestion will require an interdisciplinary approach, and will advance the development of new functional food products.

Parallels between Digestion Processes and Engineering Unit Operations

Although the study of food and drug behavior during digestion may not initially seem like an engineering system, almost all of the fundamental processes that occur in the gastrointestinal tract are similar to unit operations commonly found in the food and chemical engineering industries (Figure 1). Unit operations such as particle comminution, mixing, transport, filtration, and fermentation all take place each time a food product is consumed.

During the description of food digestion processes, it may be useful to take an engineering approach and use previously developed models, parameters, and dimensionless numbers. This will allow for greater comparison between experiments and will eliminate the need to develop completely new approaches for quantitative description of digestion processes. In the section that follows we have given a comparison of food digestion processes to typical unit operations in the food and chemical industry to facilitate the development of a quantitative framework for description of digestion processes in future studies.

Food digestion as an engineering process

Digestion starts in the mouth, where food enters the gastrointestinal tract. In the mouth, the mastication and shearing action of the tongue causes physical degradation of the ingested bite of food. This particle breakdown is similar to industrial size reduction operations, such as crushing with a jaw crusher, or grinding with a hammer mill (McCabe and others 2005). Lubrication with saliva and mixing through the extensive action of the tongue and palate transform the food into a bolus (Shama and Sherman 1973; Hutchings and Lilliford 1988). Bolus formation is similar to mixing of solid and liquid ingredients, such as forming a dough in food processing. Saliva is about 99% water in addition to various electrolytes, including sodium, potassium, calcium, and bicarbonate, mucins, and enzymes (de Almeida and others 2008). The key enzyme found in saliva is salivary α-amylase, which will enzymatically break down starch, hydrolyzing α-1,4 glycosidic bonds (Pedersen and others 2002).

From the mouth, the bolus is swallowed and passes through the esophagus. The bolus is transported through the esophagus via peristaltic muscular contractions, which will result in a similar motion to peristaltic pumping of a fluid in a processing plant. Following esophageal transit, the bolus enters the stomach, a J-shaped vessel that acts as a mixer, bioreactor, and the storage area of the digestive tract. In the stomach the bolus is mixed with gastric secretions, a blend of electrolytes, enzymes (pepsin, gastric lipase), mucus, intrinsic factor, and HCl, at an initial pH of about 1.5 to 2 (Guyton and Hall 2006). Mixing is facilitated through the peristaltic contractions of the muscular walls of the stomach. Gastric mixing is nonhomogeneous and plays a key role in the processes of gastric digestion, including the rate of breakdown, pH distribution, and gastric emptying (Guyton and Hall 2006; Edwards and Garcia 2009; Bornhorst and others 2014b). As a result of mixing, the pH gradually decreases (to about 2) resulting in inactivation of salivary α-amylase (optimum pH 6 to 7) and simultaneous activation of gastric enzymes, such as pepsin (optimum pH 2 to 4). During mixing, the stomach also acts as a bioreactor, allowing for the hydrolysis of its contents by both acid and enzymes. The

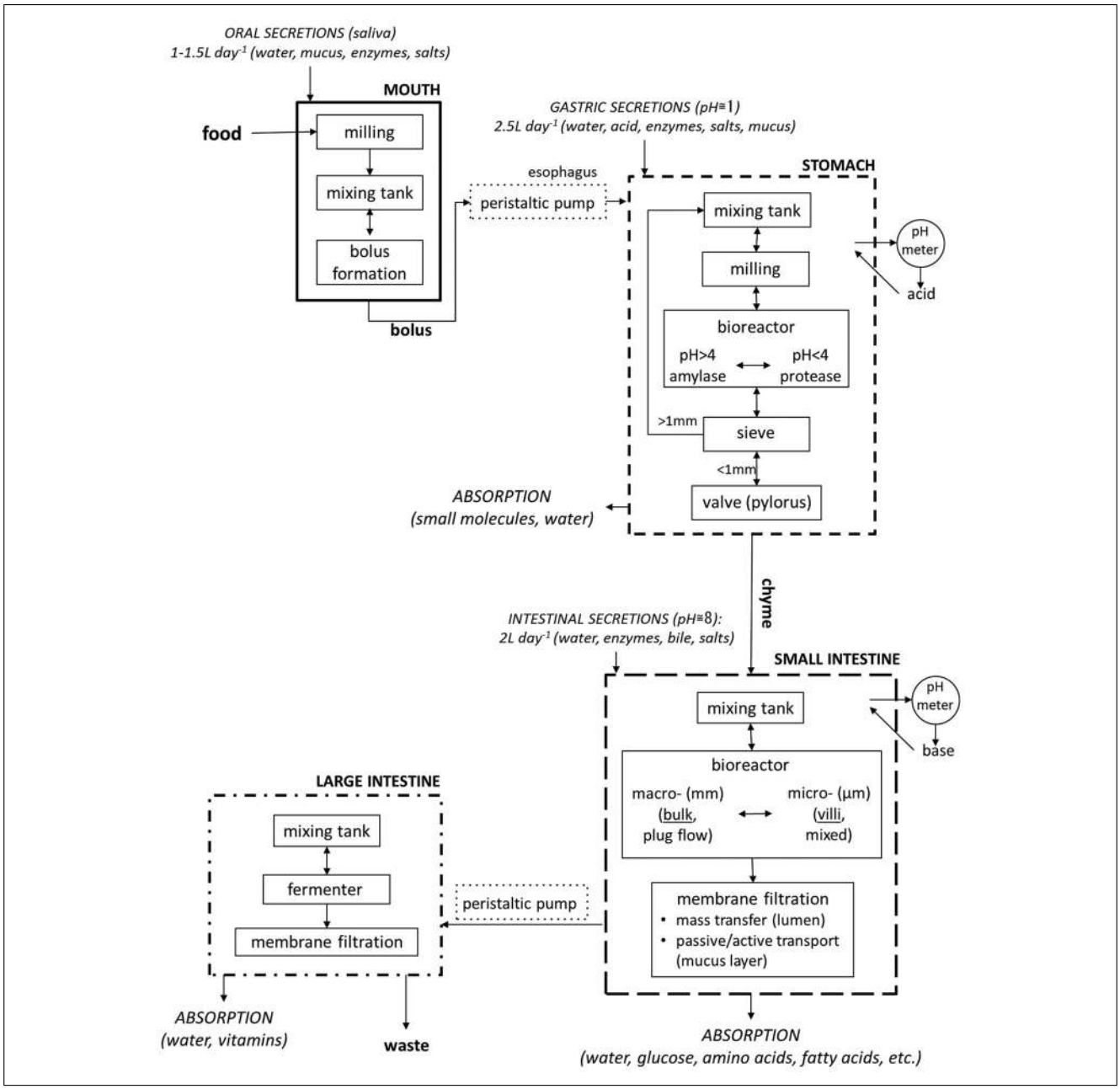

Figure 1–Process flow diagram of human food gastrointestinal digestion. Ingested food enters the mouth and passes via the esophagus to the stomach, small intestine, and large intestine. The different boxes show the various unit operations that occur during each digestion process. In the diagram, the box for each organ (mouth, stomach, small intestine, and large intestine) is represented with a different line style (solid, short dash, long dash, and dash-dot, respectively) and peristaltic propagation of food digesta is outlined with a dotted line. The food pathway is highlighted in bold letters, while secretions and absorbed material are shown in italics. Approximately 80% of the absorption occurs in the small intestine, however some compounds are absorbed in the stomach and large intestine.

gastric pH is regulated through a complex feedback-control system, similar to how many industrial processes are regulated. The result of gastric mixing is similar to what occurs in a mixing tank. In this case, the result of mixing may be similar although the driving force behind the mixing process varies (for example, impeller-driven mixing in a tank compared with peristaltic contraction-driven mixing in the stomach) (McCabe and others 2005).

In addition to mixing, chemical breakdown, and pH regulation, the stomach is also responsible for the remaining physical breakdown of the food particles present in the bolus. This breakdown occurs as a result of the pressure and physical forces exerted on the particles from the peristaltic muscular contractions in the gastric antrum (antral contraction waves) (Bornhorst and Singh 2014). This particle breakdown is similar to an industrial grinding or milling process (for example, rice milling), as it involves shear and impact forces to break down particles (McCabe and others 2005; Bornhorst and others 2013a). At the distal end of the stomach, the pylorus acts as a sieve and a valve that only allows particles of characteristic dimension of approximately < 1 mm to pass through and enter the small intestine (Barrett 2013), representing a size separation operation.

In the small intestine, chyme (as the digested food is called at this stage) is mixed with intestinal secretions. As with the stomach, mixing is nonhomogeneous and is generated by the muscular contractions of the intestinal wall, which include both peristaltic and segmentation movements (Vu and others 2009). Chyme propagates via peristaltic contractions. Segmentation contractions are the result of stretching and contraction of the intestinal wall, resulting in localized concentric recirculation of chyme, which facilitates mixing with intestinal secretions and promotes nutrient absorption through contact with the intestinal wall (Guyton and Hall 2006; Campbell 2009). Micromixing is induced in the vicinity of the intestinal wall by the motion of villi, further aiding mass transfer and enzyme action (some enzymes reside on the gut wall) (Stoll and others 2000; Wang and others 2010; Lentle and others 2013). These mixing and transport processes result in similar outcomes as industrial mixing tanks and peristaltic pumping operations.

As a result of mixing in the small intestine, pH gradually increases to alkaline, and chyme is further broken down by the enzymatic action of pancreatic enzymes, such as lipase, phospholipase A, amylase, amyloglucosidase, trypsin, chymotrypsin, carboxypeptidase, and elastase (Barrett 2013; Bornhorst and Singh 2014). Bile salts are necessary for the digestion of lipid material (Wilde and Chu 2011). Enzymatic hydrolysis of chyme is a similar process to what occurs in an industrial bioreactor, where inputs are mixed with enzymes, resulting in sugar monomers or other end products (Riedlberger and Weuster-Botz 2012).

The small intestine is the region where the majority of absorption (approximately 80%) occurs through different mechanisms, such as active and passive transport. Mass transfer may significantly impact intestinal digestion and rate/extent of absorption, offering the potential to control postprandial response by controlling mass transfer (Edwards and Garcia 2009; Gidley 2013). Nutrients and water diffuse through the mucus layer that covers the gut wall and are further transported from the lumen through the cell membrane of the mucosal epithelium (facilitated/passive diffusion) to the enterocytes and eventually to the blood stream (Guyton and Hall 2006; Barrett 2013). Absorption of water and nutrients is similar to membrane separation processes, where molecules and liquids are separated based on their specific physical and chemical properties.

The large intestine is the body's fermenter, and it is also the region where the final absorption (water and some vitamins) occurs and waste material is converted into feces. Mixing and propagation in the colon is induced similarly to the small intestine by segmentation contractions and peristaltic waves (Misiewicz 1975). Chyme mixing and transport in the large intestine can also be related to mixing in a tank and peristaltic pumping. Fermentation of any remaining, unabsorbed food particles occurs by the large microbial population (approximately 10^{10} microorganisms/g intestinal content) present in the large intestine (Bornhorst and Singh 2014). Although the substrates and products are different, this fermentation process is similar to what occurs in fermentation bioreactors, where fermentable sugars are converted into other by-products (Chen and others 2012).

Table 1–Summary of food digestion processes and their parallel unit operations from the food and chemical processing industries.

Location	Process	Related unit operation
Mouth	Mastication	Crushing, grinding
	Bolus formation	Mixing of solid and liquid ingredients (dough formation)
Esophagus	Bolus transport	Peristaltic pumping
Stomach	Particle breakdown	Grinding, milling
	Mixing	Agitated tank/mixing vessel
	pH regulation	Feedback control system
	Acid/Enzymatic hydrolysis	Bioreactor
	Gastric emptying	Sieving, size separation
Small Intestine	Chyme transport	Peristaltic pumping
	Mixing	Agitated tank/mixing vessel
	Enzymatic Hydrolysis	Bioreactor
	Absorption	Membrane filtration
Large Intestine	Chyme transport	Peristaltic pumping
	Mixing	Agitated tank/mixing vessel
	Fermentation	Fermentation reactor
	Absorption	Membrane filtration

Food digestion is far from straightforward, as it involves several steps, each comprising of multiple processes (Figure 1). Although the domain, inputs, and outputs may be quite different from traditional food and chemical engineering industries, almost all of the processes involved in food digestion have a parallel unit operation (Table 1). In future characterization of the individual (and combined) processes of food digestion, parallels can be drawn to these traditional unit operations to allow for a more in depth quantitative process description.

Characterization of food digestion unit operations

Similar to traditional food and chemical engineering unit operations, food digestion processes can be quantified using a variety of characterization parameters and dimensionless numbers. However, in contrast to industrial unit operations, many of the key input variables in digestion processes are difficult to measure and impossible to control. As such, until recently, gastrointestinal digestion has been described largely qualitatively. In order to facilitate further quantitative description and characterization of digestion processes, a summary of input variables and characterization parameters that have been used for industrial unit operations are given in Table 2. These input variables and characterization parameters may be used and adapted to appropriately describe the related digestion processes.

Several previous studies have used certain types of numerical and experimental characterization methods to describe different aspects of gastrointestinal digestion. For example, the size

Table 2–Key inputs and example characterization parameters for unit operations involved in the digestion process (Heldman and Lund 2007; McCabe and others 2005).

Unit operation	Related digestion process	Key variables	Characterization parameters and key phenomena
Size reduction (crushing, grinding, milling)	Mastication, gastric particle size reduction	Degree of size reduction (initial and final particle size) Mass flow rate of particles	Power required Work index Grinding rate function Breakage function Particle size distribution
Mixing	Gastric, small intestinal, and large intestinal mixing	Type of mixer impeller Impeller angular velocity Viscosity & presence of particles	Concentration standard deviation Mixing index (dimensionless) Mixer power number (dimensionless) Mixing time Residence time Schmidt number (dimensionless) Reynolds number (dimensionless)
Pumping	Peristaltic pumping	Velocity Viscosity Tube radius	Reynolds number (dimensionless)
Size separation (sieving)	Gastric emptying (pyloric sphincter)	Size of particles Mass flow rate of particles Capacity of screen/sieve Area of screen/sieve	Efficiency Mass flow rate for particles of different sizes
Enzymatic bioreactor	Gastric hydrolysis, small intestinal hydrolysis	Enzyme concentration Degree of mixing Particle size/form of substrate	Hydrolysis kinetics Quantity of end products
Fermentation bioreactor	Large intestinal fermentation	Microbial population Microbial community Degree of mixing Particle size/form of substrate	Fermentation kinetics Quantity of fermentation by-products
Membrane filtration	Small and large intestinal absorption	Flow rate Concentration Membrane particle size Transmembrane pressure	Permeate concentration Volumetric, solute, and rejection flux Maximum rejection conditions Permeability coefficient ratio Sherwood number (dimensionless)

reduction operation (that is, particle breakdown) during mastication has been described by modeling the particle size distribution using the Rosin–Rammler distribution function; this function was originally used to describe properties of cement (Rosin and Rammler 1933). However, multiple studies have shown that the Rosin–Rammler function provides a good fit to the particle size distribution of food during mastication, including Optosil (an artificial test food), peanuts, and peanuts inside a gel or chocolate matrix (Olthoff and others 1984; Hutchings and others 2011).

The mixing process of solid particles during gastric digestion has been previously described using a mixing index for four types of soft and rigid food particles (Bornhorst and others 2014b). In this study, the mixing of white rice, brown rice, raw almonds, and roasted almonds was monitored in the growing pig by labeling the meal with one of two indigestible markers, which were used to determine the mixing index of the meal. The mixing index was based on statistical variations in the standard deviation of the marker concentration at various sampling locations throughout the stomach. A mixing index value of one equals a sample that is not mixed and a value of zero equals a fully mixed sample. After 8 h of digestion, white rice had a mixing index of 0.06 (almost fully mixed), whereas roasted almonds had a mixing index of 0.37 (less mixing had occurred). It was determined that the type of particle (that is, soft or rigid) influenced the meal mixing, but that the gastric emptying rate of the meal also played a crucial role in the gastric mixing process (Bornhorst and others 2014b).

Mixing in the stomach or intestines may also be characterized by using a residence time distribution, similar to what may be used in an industrial mixer. Typically, a number of measures are used in reactors to characterize mixing, including scale of segregation and mixing intensity (Levenspiel 1999). A common way to characterize axial mixing and deviations from ideality is residence time distribution. Similarly, during gastric digestion, half emptying time is used to characterize the time food spends in the gastric environment. Gastric emptying half time (that is, residence time) can be measured using scintigraphy, MRI, or plasma analysis *in vivo*, and will vary based on food type. For example, a recent study using MRI showed that equicaloric meals of whole meal bread compared to rice pudding had different gastric half emptying times (for example, whole meal bread half emptying time of 132 ± 8 min compared with rice pudding half emptying time of 104 ± 7 min) (Marciani and others 2013). Gastric half emptying time may also be altered due to certain diseases such as gastroparesis, antral gastric ulcers, duodenal ulcers, and functional dyspepsia and is an important parameter in diagnosis and treatment of these conditions in the medical field (Griffith and others 1968; Janssens and others 1990; Stanghellini and others 1996; McCallum and others 1998).

Additionally, several studies have used dynamic *in vitro* model systems to complete an analysis of the mass transfer phenomena that occur in the small intestine (Tharakan and others 2010; Gouseti and others 2014). These studies determined several

Table 3–Example length scales associated with digestion, including both physical and chemical processes occurring at each length scale in each step of the gastrointestinal digestion process.

Length Scale	Macro-		Micro-	Nano- (and sub nano-)
size	cm	mm	μm	nm
Oral Digestion	Bite, Mastication, Bolus, Formation	Hydration, Texture perception	Enzymatic hydrolysis	Flavor perception
Gastric Digestion	Peristalsis	pH decrease	Enzymatic hydrolysis	Absorption
Small Intestinal Digestion	Peristalsis, Segmentation	pH increase	Enzymatic hydrolysis, Micro-mixing (villi), Diffusion through mucus layer	Absorption
Large Intestinal Digestion	Peristalsis, Segmentation		Fermentation	Absorption

dimensionless numbers (Reynolds number, Sherwood number, Schmidt number) to describe mixing and absorption in the small intestine. Through this analysis, it was found that segmentation increased mass transfer processes (Tharakan and others 2010) and that the viscosity of intestinal contents determined the relative rate of convective compared with diffusive mass transport processes (Gouseti and others 2014). By utilizing quantitative approaches, the studies described above have facilitated a greater understanding of the mechanisms and underlying phenomena that drive the food digestion process.

Although the studies described above have characterized several digestion processes quantitatively, these studies are limited, as the measurement of input and output variables in digestion processes poses significant experimental challenges. In *in vivo* systems, certain parameters, such as gastric viscosity or particle size distribution, may be difficult or impossible to measure. For certain input variables, animal models or *in vitro* systems can be used to overcome experimental limitations of *in vivo* human models. Additionally, *in vitro* systems can facilitate testing of many types of food products with larger number of replicate samples. Noninvasive imaging techniques, such as MRI and particle imaging velocimetry (PIV), are good alternatives to measure fluid flow and mixing in both *in vitro* and *in vivo* systems (Marciani and others 2001a; Tharakan and others 2010).

Multiscale Processes of Food Digestion

Length scale definition and/scope

An interesting challenge in studying food digestion is the range of length scales involved, both independently and as interrelated parts of the digestive system and the ingested foods. For the purpose of this review, the length scales will be defined as follows: macroscale refers to cm or mm sized structures or processes, microscale refers to μm sized structures or processes, nanoscale refers to nm sized structures or processes, and sub-nanoscale refers to anything smaller than 1 nm. Table 3 presents a broad classification of digestive events by section of the gastrointestinal tract and by size.

It should be noted that some processes are relevant to more than one length scale, and in these cases the largest most relevant dimension was selected. For example, while pH refers to hydrogen ions (sub-nanoscale), gastrointestinal pH changes are mainly the result of mixing at the mm scale (macroscale). For this reason, pH changes have been categorized as macroscale. Similarly, enzymatic reactions take place in the atomic/molecular level (sub-nanoscale), however the substrates are often organized in arrangements of the μm size (microscale). Therefore, while Table 3 offers a guideline and indicates the importance of length scales in digestion, care should be taken in its interpretation.

As has been shown in Table 3, all food digestion processes involve multiple length scales, some of which may be interrelated. For example, the small intestine extends in at least four length scales ranging from the luminal diameter (cm-mm) to the organizations of the villi on the epithelial wall (mm), to the lining of the epithelial wall with a villi layer (μm), down to the dimensions of a single villus, the mucus layer, and the sites of nutrient transport in the cell membrane (nm and <1 nm) (Guyton and Hall 2006; Stoll and others 2000; Love and others 2013).

If the entire process of food digestion is considered, it can be observed that the multiscale aspect of the process is present during all steps of digestion. During mastication in the oral cavity, texture is perceived by the action of tongue and palate (mm), while salivary α-amylase attacks chemical bonds in starches (μm). Flavors are typically sensed by the action of molecules on the tongue's taste buds (nm). In the stomach, peristaltic contractions mix the bolus with gastric secretions and food particles are broken down (cm-mm). At the same time, pH decreases, enzymes hydrolyze food digesta, and limited molecular absorption occurs (mm-μm). Interestingly, mixing the small intestine is important in both macroscale (segmentation, cm) as well as microscale at the vicinity of the villi (μm), and the coupling between these two characteristic dimensions is an active research area. As a result of mixing, the luminal pH increases (mm-μm), enzymes hydrolyze the chyme, the products diffuse through the mucus layer (μm-nm), and nutrients are absorbed through the cell membrane (nm). In the large intestine, segmentation (cm) further mixes the luminal contents, bacteria ferment nonabsorbed material (μm), and some final absorption occurs (nm). Feces are eventually formed and excreted from the body (cm).

Similarly, ingested foods have structural arrangements ranging across several orders of magnitude, and are highly heterogeneous materials. The length scales involved in food products range from cm (for example, bite size of solid foods), to mm (for example, food powders), to μm (for example, emulsion droplets, foam bubbles, crystals), to nm (for example, plant cell walls, gelled proteins), down to single nutrients of the angstrom regime (for example, glucose, water) (Aguilera 2005). The functionality and digestibility of foods strongly depends on interactions between the length scales, which trigger different physiological responses. Naturally, consideration of phenomena at different length scales, as well as their interactions, is crucial in a comprehensive study of food digestion.

Another determining factor in the digestion process is time. For example, controlled release of sodium ions may trigger saltiness perception at lower salt levels, slower gastric emptying may prolong the sensation of satiety, and reduced mixing in the small intestine may control the rate and extent of nutrient absorption (de Loubens and others 2011; Mills and others 2011; Fiszman and Varela 2013; Gidley 2013). Although time does play an important

role in the digestion and absorption processes, the influence of time will not be specifically considered in the discussion that follows.

Case studies illustrating different length scales of digestion

The length scales outlined in Table 3 play an important role in the entire gastrointestinal digestion process. Case studies that further illustrate digestion of different initial food matrices at these varying dimensions will be discussed below. These case studies are not meant to be inclusive examples of all possible length scales involved in the digestion process, rather, to give specific examples of the different length scales involved in digestion and absorption of various nutrients and food systems.

Hydrogel digestion. A full stomach signals an increased sense of satiety and a decreased sense of hunger, as fullness has been shown to be correlated with larger gastric volume *in vivo* (Marciani and others 2001b). Prolonging stomach fullness may therefore aid in controlling weight gain and addressing diseases such as obesity. One suggested way to prolong satiety after food ingestion is the incorporation of structures/particles that gel under the acidic gastric conditions, or gels that remain stable during gastric digestion and have varying fracture strengths (Norton and others 2006; Edwards and Garcia 2009; Fiszman and Varela 2013; Gidley 2013).

Hydrogel formation (macroscale). One hydrogel that forms both an ionic and acidic gel is alginate. Alginate is a linked co-polymer of β-1,4-linked D-mannuronic acid and α-1,4-linked guluronic acid. It will form an ionic gel in the presence of multivalent cations (for example, Ca^{2+}) and an acidic gel at pH values less than the pK_a of the uronic acid residues (Hoad and others 2004). Alginate gels have been studied *in vivo* using MRI, as viscous gel solutions and as preformed gel beads. Alginate solutions were shown to form gel "lumps" in the stomach. These lumps were formed near the wall, presumably where the gel came in contact with gastric acid (Figure 2A). Consequently, alginate solutions forming strong acidic gels resulted in decreased hunger and increased fullness 115 min after the meal (Hoad and others 2004). Similarly, when subjects were fed meals of alginate gel beads (approximately 4 mm) that would form either a strong or weak acidic gel, gastric sieving of the strong gel beads was observed, as the volume of strong gel beads in the stomach was greater than the volume of weak gel beads 60 min after ingestion (Hoad and others 2009; Rayment and others 2009). These studies indicate that the gel-structures formed by alginate at the macroscale (mm-cm) influence digestion processes such as gastric emptying and satiety. Similar gelling behavior of alginate and other hydrocolloids has been obtained *in vitro* (Knarr and others 2012; Bradbeer and others 2014; Zhang and others 2014).

Hydrogel strength (microscale). The presence of macroscale gelled structures or particles in the stomach has been shown to be important for satiety, but the specific properties of the gels or particles, impacted by microstructure, also play a role in their functionality. Gellan gum is another gum that has demonstrated pH-dependent gelling properties *in vitro*. In gellan gum gels, the microstructural changes were influenced by pH (Figure 2B). These microscale changes influenced the macroscale gel properties, such as failure stress. Gradually denser gels with smaller pores were observed as pH decreased from 4.0 to 2.5 (Yamamoto and Cunha 2007). As the gel structure became denser, the gel showed higher failure stress. At lower pH (2.0) the gels became more elongated with evident defects and lower failure stresses. This case study shows an example of various interrelated length scales. As demonstrated by these case studies, both gel macrostructure and microstructure will impact its properties and behavior during gastric digestion. These examples demonstrate that it is crucial to examine as many of the involved length scales as is feasible in a digestion study to understand the controlling structures and processes.

Lipid digestion. Release and absorption of dietary lipids takes place across multiple length scales, from macro- to nanoscale. For nutrients to be absorbed, they must first be released from the food matrix, whether the matrix is a natural food structure (for example, plant cell walls) or a processed food matrix (for example, emulsion). Once lipids are released from the food matrix, their digestion involves hydrolysis of triacylglycerides to di- and monoacylglycerides and free fatty acids. This reaction requires close proximity of the enzyme (lipase) with the substrate at catalytic conformation. The rate and extent of reaction depends on the accessibility of lipase, the specific surface area, and the interfacial properties of the droplets (Chu and others 2010; McClements and Li 2010; Reis and others 2009; Joyce and others 2014). At the molecular level, displacement of the adsorbed stabilizing layer of the oil droplets is required for lipase to access the lipid substrate before the hydrolytic reaction can take place. Bile salts play a key role in this mechanism, as they are essentially a group of surface active substances that facilitate lipid digestion by enhancing enzyme accessibility. The action of bile salts, and therefore the rate and extent of lipid digestion, is affected by the molecular packing of the interface between the oil droplets and the digestive fluids (Mun and others 2006; McClements and others 2008; Sarkar and others 2010).

Lipid release (macroscale). The almond cell wall structure has been shown to play a major role in the release and absorption of nutrients from almonds, including lipids and vitamin E (Mandalari and others 2008; Mandalari and others 2014). In both *in vivo* and *in vitro* studies, the rigid structure and robustness of almond cell walls has been shown to effectively encapsulate nutrients and limit their release and absorption. During an *in vitro* gastric and duodenal digestion study, finely ground almonds had a greater release of lipid, protein, and vitamin E compared to raw almonds (Mandalari and others 2008). It was hypothesized that during the physical breakdown of the almond matrix (that is, grinding), cell walls were ruptured, leading to increased release of encapsulated nutrients during *in vitro* digestion (Figure 2C). Similar findings have been reported *in vivo*, with decreased chewing (that is, less macrostructural breakdown) being proportional to increased fecal energy and fat losses after consumption of almonds (Cassady and others 2009). These studies show the importance of the food macrostructure in controlling the food breakdown and nutrient release during digestion, both *in vivo* and *in vitro*.

Lipid hydrolysis (microscale). Once released from the macroscale food matrix, lipid digestibility may additionally be controlled by enhancing or inhibiting access to the lipid by enzymes (Mun and others 2006; Hu and others 2009; McClements and Li 2010). For example, encapsulating oil droplets in large (>100 μm) beads resulted in reduced oil digestibility during *in vitro* digestion (Li and McClements 2011). In this study, lipid droplets were either not encapsulated (control) or coated with an alginate layer, then trapped in a chitosan/calcium alginate coacervates, resulting in the formation of small (<50 μm in diameter) or large (>100 μm in diameter) beads. Non encapsulated drops were initially homogeneously suspended into the continuous phase and fully digested after the simulated digestion process. Encapsulation resulted in clustering of the droplets in larger assemblies, the effect being more appreciable with increasing bead size. After *in vitro* digestion, large (>100 μm) beads showed evident signs of nondigested lipids (Figure 2D). This study demonstrates that even

within a length scale (for example, microscale), size differences influence structuring and digestion of nutrients.

Starch digestion. Starch is a major carbohydrate in the human diet, estimated to contribute about 50% to 70% of humans total energy intake (Copeland and others 2009). Rice is commonly consumed as either brown or white. White rice is the processed counterpart of brown rice; in white rice, the outer bran layer of brown rice has been removed through a milling process. Aside from differences in macrostructure between brown and white rice, different varieties (that is, long grain, medium grain, short grain) of rice have different amylose:amylopectin ratios (Bornhorst and others 2014a), which impact the starch microstructure. In its native form, starch is arranged in granules of various sizes (1 to 100 μm) and shapes, principally containing amylose and amylopectin, two glucose polymers (Tester and others 2004; Copeland and others 2009). Starch granules are semi-crystalline materials with microstructures showing semi-crystalline rings, comprised of crystalline and amorphous lamellae and amorphous rings (Jenkins and Donald 1995; Buléon and others 1998). The crystalline regions have been associated with the amylopectin component (Buléon and others 1998; Jenkins and Donald 1995; Tester and others 2004). Digestion of starch could be studied as a solid-liquid two phase reaction, where amylase must (i) diffuse into the food matrix, (ii) bind the substrate, and (iii) cleave the glycosidic linkages of the starch molecules (Leloup and others 1991; Zhang and others 2009).

Starch release (macroscale). The differences between brown and white rice due to the presence/absence of the bran layer of rice during digestion has been investigated *in vitro* as well as in an *in vivo,* using the growing pig as a model for an adult human (Bornhorst and others 2013a; Bornhorst and others 2014a; Mennah-Govela and others 2015). By using rice of the same variety, the influence of specific starch microstructure can be eliminated, as the rice starch will be the same in both brown and white rice samples. Examination of the gastric contents of pigs that had consumed a meal of only white or brown rice (var. *Calrose*, a medium grain rice) showed no significant differences in the gastric emptying of dry matter or starch between the two rice types. However, brown rice exhibited significantly slower protein emptying, hypothesized to be due to removal of the bran layer in the stomach through a gastric milling process (Figure 2E). The rice bran layer played a crucial role in the rice breakdown, modifying the rice buffering capacity, which influenced the quantity of gastric secretions, as well as delaying changes in rheological properties and rice grain texture (Bornhorst and others 2013a, b). Differences between brown and white rice of the same variety have also been observed *in vitro*, with brown rice exhibiting slower decrease in grain texture when incubated with simulated saliva, but having a faster effective diffusivity of gastric juice into the bolus compared to white rice (Bornhorst and others 2014a; Mennah-Govela and others 2015). These studies show the importance of the rice macrostructure on the breakdown phenomena and physiological response to rice during digestion.

Starch hydrolysis (microscale). Different starches naturally occur between and within plants varying in form and functionality. Starches show different digestion patterns depending on their size, crystallinity, and amylose:amylopectin ratio (Blazek and Copeland 2010). Figure 2 shows an example of different mechanisms of digestion for a low amylose (also known as waxy, <2% amylose) and high amylose (42% amylose) starch after 2 h of *in vitro* incubation with α-amylase (Blazek and Copeland 2010). α-amylase is known to preferentially hydrolyze amorphous, high in amylose regions. In waxy starches, where the small amount of amylose is distributed throughout the granule, digestion appeared to occur "from inside out," and the enzyme removed parts of the structure producing holes that allowed access to the inner part of the granule. The granule itself retained its shape and size, and became less dense (Figure 2F). By contrast, the mechanism of digestion for high amylose granules seemed to be "from outside in" (or "all-or-none"), where smaller granules of unchanged density were observed (Blazek and Copeland 2010). Compared to waxy starch, the high amylose starch showed faster digestion rates by 40%, indicating different properties depending on the starch composition and structure. The importance of starch form has led to the development

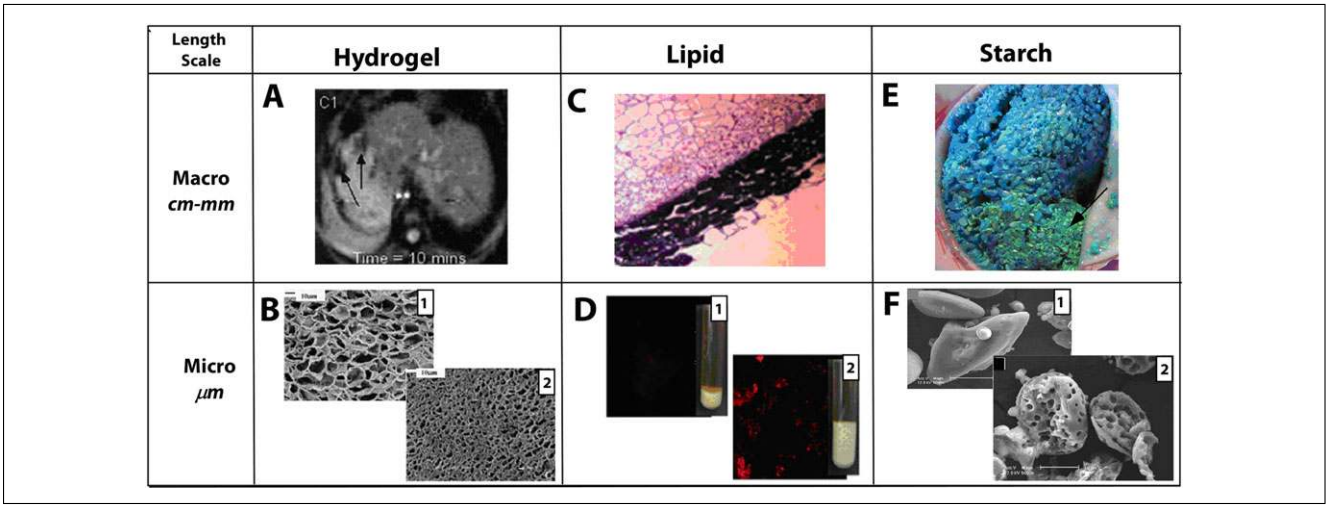

Figure 2–Example images showing the range of length scales in hydrogel, lipid, and starch food systems. In hydrogel systems, macro-sized gel beads can be seen in a magnetic resonance image of the human stomach after consumption of alginate solutions (A) (Hoad and others 2004). Gellan gel microstructure at pH 4 (B1) and pH 3 (B2) (Yamamoto and Cunha 2007). In lipid digestion, the outer layer of cells in an almond matrix have been ruptured during *in vitro* gastric and duodenal digestion (C) (Mandalari and others 2008). Lipid encapsulated in beads of <50 μm (D1) and >100 μm (D2) hydrogel beads after *in vitro* digestion, showing different structures as influenced by the microscale size (Li and McClements 2011). In starch digestion, the accumulation of the bran layer during the starch release process in brown rice (E) adapted from Bornhorst and others (2013a). Starch granule degradation in low (F1) and high (F2) amylose starches after 2 h incubation with α-amylase (Blazek and Copeland 2010).

of physically, chemically, and recently genetically modified species that have structures with the desired characteristics (Bemiller 1997; Jung and others 2012). These case studies demonstrate the impact of the release of starch from the macrostructure and the influence of microstructure in starch release, hydrolysis, and absorption.

Challenges and Future Recommendations

Gastrointestinal digestion is a complex process that is influenced by phenomena occurring at several length scales. In many cases, it is difficult to isolate these multiscale phenomena and their influences on the food digestion process. With this in mind, food digestion studies should be designed to focus on the process-controlling length scale, but should still consider the effect of other length scales, if possible. The multiscale aspect of food digestion must be considered to allow for a comprehensive process description. Here we have identified specific gastrointestinal processes at these varying length scales and given case studies to demonstrate the importance of multiple length scales, and their interrelated nature, in the breakdown, release, hydrolysis, and absorption of various dietary substances.

Additionally, to facilitate description and quantitation of gastrointestinal digestion processes, analogs to traditional engineering unit operations have been given, along with typical input variables and characterization parameters. However, in contrast to unit operations in the food and chemical industry, food digestion processes often have inputs and parameters that are difficult to measure and may be impossible to control *in vivo*. For this reason, along with decreased resource and ethical considerations, *in vitro* models may be more commonly used in the laboratory to mechanistically study the phenomena taking place during food digestion.

In the future, the multiscale aspect of digestion should be considered in designing both *in vitro* and *in vivo* studies. If possible, integration of phenomena occurring at multiple length scales should be studied. Until recently, quantitative descriptions of food digestion processes were scarce in the literature. As a result of advances in noninvasive imaging technologies, recent progress has been made in quantitatively describing aspects of the digestion process, such as the rate of contractions in the gastric antrum. Suggestions have been made here as to engineering analogs of many of the processes occurring during gastrointestinal digestion. Future descriptions of the digestion process may be based on engineering analyses of other traditional unit operations to allow for comparisons to be easily made across studies and experimental conditions. By using a combination of *in vitro* and *in vivo* studies that link multiple length scales to provide a quantitative analysis of food digestion processes, our knowledge of food digestion will be greatly increased. Using this systems-based, multiscale approach, we will gain knowledge that will facilitate food product development to optimize functional food properties.

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