Disintegration of Solid Foods in Human Stomach

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ABSTRACT: Knowledge of the disintegration of solid foods in human stomach is essential to assess the bioavailability of nutrients in the gastrointestinal (GI) tract. A comprehensive review of food gastric digestion, focusing on disintegration of solid foods, is presented. Most of the research reviewed in this paper is contained in the medical, pharmaceutical, food, and nutritional literature. Stomach physiology is briefly introduced, including composition and rheological properties of gastric contents, stomach wall motility in fed/fasted states, and hydrodynamic and mechanical forces that act on the ingested food. *In vivo* and *in vitro* methods used for studying food and drug digestion in GI are summarized. Stomach emptying rate, which controls the rate of absorption of nutrients, is highly related to the disintegration of foods. This topic is highlighted with focus on the important mechanisms and the influence of chemical and physical properties of foods. Future research in this area is identified to increase our fundamental understanding of the food digestion process in the stomach as related to the food composition, material properties such as texture and microstructure, and chemical characteristics. This information is necessary to develop new guidelines for seeking innovative processing methods to manufacture foods specifically targeted for health.

Keywords: controlled release, digestion, food disintegration, gastric emptying, stomach

Introduction

Food digestion in the GI tract

In the human digestive process, foods undergo major size reduction to help release embedded nutrients so that they may easily pass into the bloodstream for eventual absorption by the body cells. Mouth and stomach are the major compartments where foods are disintegrated into small size, whereas small intestines are the major site of nutrient absorption. In the digestive tract, both mechanical forces and chemical reactions break down ingested food into small molecules. The rate kinetics of digestion depends on the chemical and physical characteristics of food and their interaction with the physiological events occurring within the gastrointestinal (GI) tract.

Digestion of foods begins with chewing in the mouth. The oral step is rapid but plays an important role in digestion. Mouth secretes saliva containing mucus and the enzyme amylase. Mastication reduces the particle size, and hydrates and lubricates the food by mixing it with saliva. Mastication also reduces viscosity of starchy food by the rapid action of salivary amylase (Hoebler and others 2002). Food bolus is formed and transported through the esophagus to the stomach by the mechanism of peristalsis. Peristalsis is an advancing wave of contraction of the walls of a flexible conduit, forcing the contents forward (Siddiqui and others 1991).

The stomach is divided into 4 major regions: fundus, body, antrum, and pylorus (Figure 1). The stomach has 3 main motor functions: storage, mixing, and emptying. The proximal part made of fundus and body acts as a reservoir for undigested material, responsible for the emptying of liquids, whereas the distal stomach (antrum) is the grinder, mixer, and siever of solid food, and acts as a pump for gastric emptying of solids by propelling actions (Urbain and others 1989; Arora and others 2005). The reservoir function of stomach is achieved through the flexible volume of the stomach, which can expand to accommodate food up to a volume of about 4 L. Mixing and homogenizing function is achieved through the secretion of gastric juice and stomach contraction that produces grinding and crushing of foods. Gastric juice secreted from glands lining the stomach contains gastric acid, bile salts, and digestive enzymes. The gastric juices penetrate and dilute the food bolus. Peristaltic waves originate from the stomach wall and spread toward the antrum, mixing and forcing the antral contents toward the pylorus. The pylorus contracts to slow gastric emptying and results in further mixing of gastric contents. During this time, the stomach transforms its contents into multiphase slurry called chyme, which is a combination of separate phases of aqueous solutions, fats, and solids. The more intense peristaltic waves promote antral emptying, which allows gastric contents, mainly fluid mixed with small particles, to pass through the pylorus and enter the duodenum. The particle size of the food emptied through the pylorus is less than 1 to 2 mm during the fed state (Thomas 2006).

Final stages of digestion and most of the nutrient absorption occur in the small intestine, where the food is dissolved into the juices from the pancreas, liver, and intestine. All of the digested nutrients are absorbed through the intestinal walls. The waste products are propelled into the colon for excretion.

Digestion of solid foods may be considered as a 2-step process: disintegration and dissolution. Disintegration indicates how fast a food particulate can break into small fragments so that any entrapped nutrient ingredients can dissolve into the gastric juice. Dissolution indicates how fast nutrient ingredients can dissolve into solution for absorption. It is hypothesized that both these steps, disintegration and dissolution, can be affected or controlled by the food-processing conditions used at the manufacturing/preparation stage.

Chemical and physical transformation of solid foods in mouth

Oral mastication is the initial step in food digestion. From a physiological point of view, the main role of mastication is to

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convert a piece of food into a bolus ready for swallowing (Jalabert-Malbos and others 2007). Chewing (mastication) breaks up food into small particles, increasing the surface area for digestion and absorption. The food is then mixed with amylase-containing saliva to form a swallowable bolus for transport via esophagus into the stomach. Mastication has a significant influence on the digestive process such as gastric emptying rates. Inadequate mastication might lead to maldigestion (Pera and others 2002).

Although there is a large variability among individuals in the physiology of mastication, no interindividual variability in the particle sizes of food boluses was observed at the end of the chewing process (Peyron and others 2004; Jalabert-Malbos and others 2007). However, particle size distributions vary significantly among foods. Measurements with sieving and laser diffraction methods indicated that chewed particles were much larger in vegetables than in nuts: raw vegetables were transformed into boluses made up of particles larger than 2 mm, and nuts gave a bolus which contained 90% of particles smaller than 2 mm (Peyron and others 2004). The median particle sizes (theoretical sieve through which 50% of the particle weight can pass) for some selected foods are 0.82 mm (peanuts), 1.9 mm (carrots), 2.4 mm (Emmental), 2.68 mm (olives), and 3.04 mm (gherkins) (Jalabert-Malbos and others 2007).

The size of particles resulting from mastication depends on the food texture (Hoebler and others 2000; Foster and others 2006; Jalabert-Malbos and others 2007). Agrawal and others (1997) showed that the rate of food breakdown between the teeth, as indicated by the number of fractures and consequently the number of fragments, is inversely related to the fragmentation index given by $(R/E)^{0.5}$, where R is toughness, indicating the energy needed to generate and propagate a fracture through the sample, ranging from approximately 56.97 J/m^2 for apple pulp to 4355.45 J/m^2 for prune pit (Williams and others 2005); E is Young's modulus corresponding to the stress/strain ratio and describes the strength of the material, ranging from 0.07 MPa for gummy bears to 346 MPa for popcorn kernels (Williams and others 2005). Moreover, the fragmentation index is significantly related with muscle activities such as masticatory frequency (Foster and others 2006).

Food texture also affects starch hydrolysis in the mouth. Starch hydrolysis is twice as high for bread as for spaghetti, mainly because of the release of high-molecular-mass α-glucans (Hoebler and others 1998). After chewing, bread particles were highly degraded, with strong disruption of structure, whereas spaghetti showed incomplete reduction of particle size and limited structure loss (Hoebler and others 1998). Current investigations are actively considering the role of the product microstructure to control in-mouth behavior and delivery of molecular species, as well as flavor, taste, aftertaste, and physical sensation (Norton and others 2007).

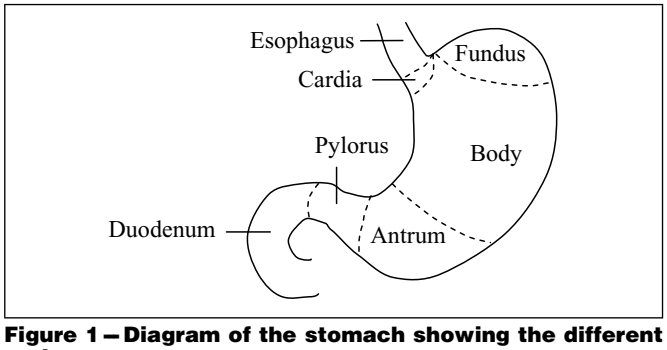

Figure 1 — Diagram of the stomach showing the different regions.

Role of gastric disintegration of solid foods

Compared with oral mastication, the gastric disintegration of foods has been less studied and thus the understanding is comparatively limited. This is partly due to the complexity of gastric digestion of foods, which involves numerous influencing factors such as fed/fast state, gastric acid, enzymatic reactions, and hydrodynamic and mechanical forces. On the other hand, stomach physiology has not been fully understood; the stomach wall movement, rheological properties of gastric content, the flow state of gastric fluid, and hydrodynamic/mechanical forces acting on foods require further clarification. Most of the studies have been connected with medical and nutritional research. Recently, the notion of healthy foods and bioavailability is gaining wide recognition (Norton and others 2007). Food microstructure (or the food matrix) plays a major role in the release and bioavailability of nutrients and allergenic substances (Norton and others 2007; Parada and Aguilera 2007). Approaches may be taken at manufacturing stage to change food structure to regulate the release of active ingredients from food. For example, an increase in the consistency of custard decreased the release of phenolic tyrosol in the mouth and stomach, whereas it did not have any effect in the intestine (Sanz and Luyten 2006). A fundamental understanding of the interaction of the food matrix and active ingredients and its performance during human GI digestion can help to develop the next generation of structured foods for health (Sanz and Luyten 2006; Norton and others 2007). Knowledge of the disintegration kinetics of foods in the human stomach is essential to assess the bioavailability of nutrients in the GI tract, and to establish processing conditions at the manufacturing stage to promote optimum and/or controlled release of nutrients in targeted regions of the GI tract.

The information will enhance understanding of stomach emptying of foods and consequently provide information to develop approaches for controlled stomach emptying. Stomach emptying is a critical step in the digestion process. Particularly, it is closely related to obesity, diabetes, and stomach disorder problems such as dyspepsia (Rayner and others 2001; Cardoso-Júnior and others 2007). Rapid emptying can reduce the negative feedback satiety signals, and thus encourage overconsumption of calories (Cardoso-Júnior and others 2007), whereas delayed gastric emptying is a crucial problem in diabetes mellitus, gastroesophageal reflux, and aging (Vaisman and others 2006). Control of gastric emptying is essential for ensuring optimal digestion. The potential for modulation of the rate of gastric emptying to control obesity and diabetic patients is being explored vigorously by the pharmaceutical industry (Rayner and others 2001). Food structure and texture have been found to affect stomach emptying. For example, studies have shown that addition of acid-instable emulsions to preprocessed foods led to accelerated gastric emptying, whereas ingestion of acid-stable emulsions delayed gastric emptying and reduced the amount of food consumed (Marciani and others 2007). In the future, foods may be structured in such a way as to control the rate of release of macronutrients and to reduce or increase the rate of stomach emptying (Norton and others 2006). A recent review provides information on how structured foods may play a role in controlling obesity (Norton and others 2007). An enhanced understanding of food disintegration in GI and its relationships with physical and chemical properties of foods may help different clinical studies through the design of specific food microstructures.

Study of food gastric disintegration should help our understanding of the interactions between food and drugs during digestion. The disintegration activity of a drug is substantially affected by the presence of food components. Food intake may attribute to elongated residence of the tablets in the proximal parts of the

stomach, resulting in delayed drug absorption and the occurrence of late high plasma peak concentrations (Collins and others 1996; Weitschies and others 2005). On the other hand, bioavailability of some drugs such as saquinavir may be significantly improved in the presence of food, due to the fed state prolonged gastric emptying time that improves exposure of the drug to target absorption sites (Kenyon and others 1998). It was recently reported that food could significantly delay drug tablet disintegration in the stomach by formation of a film around the tablet, a phenomenon that is dependent both on the tablet's ingredients and composition of the administered food (Abrahamsson and others 2004). Food may also affect the pH of gastric contents. Thus the understanding in food disintegration should help improve the control of drug dissolution in the stomach.

The objective of this paper is to provide a comprehensive review of studies on disintegration of solid foods in the gastric environment to help promote release of nutrients embedded in the food matrix. Most of the research conducted on this topic is published within the medical, pharmaceutical, and nutritional literature. Published studies in these areas have been searched for pertinent references. Stomach physiology will be briefly introduced in the beginning to define key terminology used in the review.

Stomach Physiology and Food Digestion

Composition and rheology of gastric juice

In the fasted state, resting volume of stomach is as low as 25 mL (Vertzoni and others 2005). Ingestion of food and distention of the stomach induce secretion of gastric juice. Stomach secretes 2 to 3 L of gastric juice/day. The rate of secretion may increase from 1 mL/min under fasted conditions to 10 to 50 mL/min immediately after food ingestion (Versantvoort and others 2004). Increase in food amount, protein content, and meal viscosity increases secretion (Marciani and others 2001). Principal components of gastric secretion include hydrochloric acid (HCl), pepsinogens, mucus, and water. HCl assists acid denaturation of digested food, activates pepsinogens, and kills most of the ingested bacteria. Pepsinogen is the inactive form of the enzyme pepsin, a principal enzyme of the gastric juice. It is converted to the active form by the action of gastric juice. Mucus forms a gelatinous coating over the mucosal surface. Gastric juice contains 0.8 to 1 mg/mL pepsin and about 1.5 mg/mL mucin (Vertzoni and others 2005; Dean and Ma 2007).

In the fasted state, intragastric pH in healthy subjects is in the 1.3 to 2.5 range. Eating can increase pH to a 4.5 to 5.8 range. Within 1 h after eating, the pH of the stomach decreases to less than 3.1 (Malagelada and others 1976; Dressman 1986). Food composition and quantity play a major role in deciding the time required to restore the fasting pH levels, although food pH value also has an influence (Kalantzi and others 2006). Figure 2 shows a profile of pH changes in a human stomach.

Buffer capacity, surface tension, bile salts, and osmolarity are also important for food and drug digestion. Buffer capacity of gastric contents is high in the fed compared to the fasting state, ranging from 5 to 30 mmol L^{-1} ΔpH^{-1}. Average concentration of bile salts ranges from 80 to 275 μM, the surface tension 28 to 51 mN/m, and the osmolarity 191 to 200 mOsm/kg in gastric juice. The principal cations in gastric juice are sodium (about 70 mM) and potassium (about 15 mM), whereas the principal anion is chloride (about 100 mM) (Dressman and others 1998; Vertzoni and others 2005; Kalantzi and others 2006).

Typical gastric juice in the stomach is a viscous fluid with viscosity roughly in the range 0.01 to 2 Pa.s and density close to the density of water (Marciani and others 2000; Abrahamsson and others 2005). It is non-Newtonian with pseudoplastic or shear-thinning behavior (Takahashi and Sakata 2002; Dikeman and Fahey 2006). Although ingestion of a high viscosity meal will increase the apparent viscosity of the contents of the stomach, the effect is minimized as the stomach responds to high viscosity meal ingestion by rapid intragastric dilution causing a reduction of meal viscosity. Marciani and others (2000) reported that the zero-shear viscosity (obtained from the viscosity/shear rate profiles covering 30 shear rates from 0.1 to 1000 1/s) of a meal containing 1.5 g locust bean gum per 100 g fell from 11 to 2 Pa·s immediately after ingestion, and decreased to 0.3 Pa·s after 30 min.

Evaluation of the viscosity of the stomach digesta is a difficult task. As a non-Newtonian fluid, the viscosity is associated with shear rate. The flow profile should be obtained across various shear rates rather than the estimation of viscosity at only 1 shear rate. In addition, digesta is often mixed with particulates and semisolids, which interfere with viscosity measurements. Many researchers centrifuge digesta samples prior to measuring viscosity to remove large particles from the sample (Dikeman and Fahey 2006). However, removal of solid particles from digesta could dramatically lower the viscosity of the contents (Takahashi and Sakata 2002). Omura and Steffe (2003) proposed a mixer viscometer impeller with an interrupted helical screw to evaluate the rheological properties of fluid foods with large particulates; this may be a more appropriate approach for determining rheological properties of the stomach digesta. Viscosity of gastric contents may be measured *in vivo* by echo-planar magnetic resonance imaging (EPI) (Marciani and others 2000, 2001).

Stomach motility and antral contraction

The pattern of stomach motility is distinct in the fasting and fed states. There is a 4-phase movement in the fasting state and continuous movement in the fed state. During the fasting state, the interdigestive myoelectric cycle or a migrating myoelectric cycle occurs in which interdigestive series of electrical events sweep through stomach and intestine in a regular cycle (Arora and others 2005). A cyclic contractive pattern dominates as a result of circular muscle contractions. This cycle is further divided into 4 phases according to contraction strength, and each lasts for a different period of time. Phase I lasts for 40 to 60 min with rare contraction. Phase II continues for a similar period of time with increasing frequency and

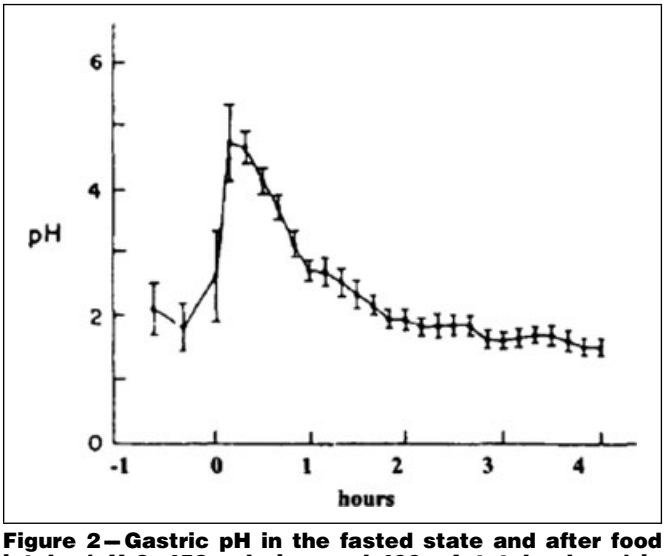

Figure 2—Gastric pH in the fasted state and after food intake (pH 6, 458 calories, and 400 mL total volume) in 10 healthy volunteers (Malagelada and others 1976).

contraction strength (up to 40 mm Hg). Phase III is short (4 to 6 min) with the highest contraction strength (up to 80 mm Hg). During phase III, all the undigested material is swept out of the stomach down to the small intestine. Phase IV is a transition period between phase III and phase I, typically lasting for 15 to 30 min. The whole cycle is repeated approximately every 2 h until ingestion of a meal.

On ingestion of a mixed meal, the pattern of contractions changes to digestive motility pattern, which is continuous with a moderate strength in the range of 15 to 20 mm Hg. There are 2 types of contractions, regular tonic contractions and peristaltic contractions. Tonic (fundic) contractions are the shallow indentations on the proximal greater curvature, which move food from the top to the bottom of the stomach (Pal and others 2007). Peristaltic contractions are mainly the result of longitudinal contraction and born of tone contractions on the upper surface of the stomach. The waves of contraction travel toward the pylorus in a sequential manner, 2 to 3 peristaltic contractions proceeding at any time (Figure 3). The contraction frequency approximates 3 cycles/min. The propagation velocity averages 2.5 mm/s, and increases from the proximal to the distal stomach. Each contraction takes approximately 1 min to advance from the fundus to the pylorus (Bilecen and others 2000; Kwiatek and others 2006; Schulze 2006).

As the peristaltic wave reaches the pylorus, the contraction width increases and indentations deepen, often virtually occluding the antral lumen, a process referred to as "terminal antral contraction" (Bilecen and others 2000; Schulze 2006). Meanwhile, the pylorus contracts and the sphincter narrows, so that the pyloric opening is small on the arrival of the peristaltic wave. The chyme is thus squirted back into the stomach, an action called retropulsion (Figure 4). Retropulsion is responsible for drastic mixing and emulsifying the food with gastric juices, causing grinding and rubbing between food particulates and/or stomach wall. Repeated propulsion, grinding, and retropulsion reduce the size of food particles into a softer consistency in a suspension form (Schwizer and others 2006). Antropyloric contractions occur and the pylorus partially opens, causing a "sieving effect" in which liquids and small particles (< 1 to 2 mm) flow continuously from the stomach into the duodenum, whereas the indigestible particles greater in size than the pyloric opening are retropelled and retained in the stomach. When the meal has finished emptying from the stomach, the fasting motility pattern is resumed. Indigestible large objects are emptied only during phase III activity (Dressman 1986).

The stomach contraction, particularly terminal antral contraction, imposes a considerable mechanical destructive force on food particulates and thus plays a significant role on the disintegration of solids. Researchers have measured contraction forces present in the stomach. Vassallo and others (1992) used a 1.8-cm balloon to measure the forces along the longitudinal axis of the distal stomach. The balloon was mounted on a tube and fixed a few

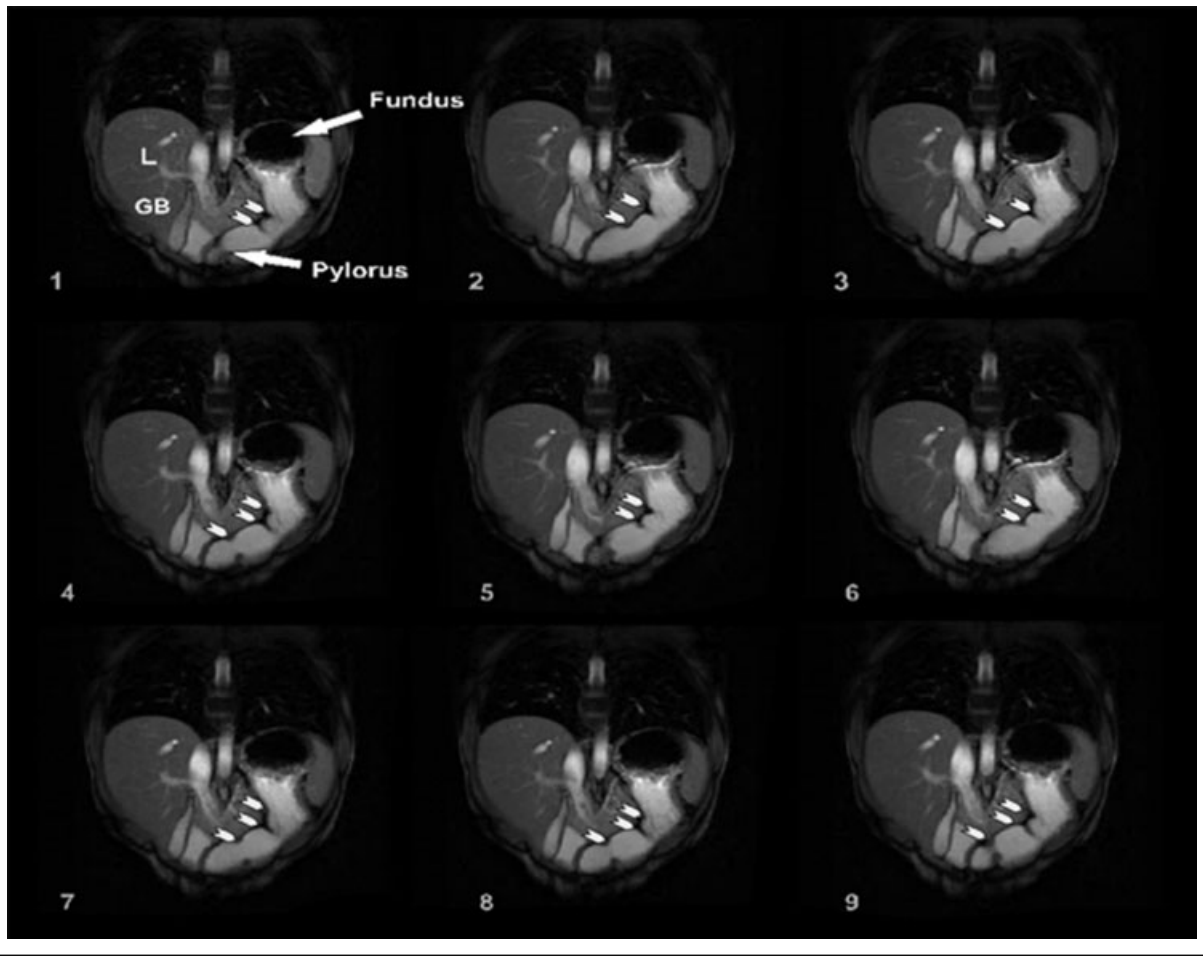

Figure 3—Dynamic MRI image series showing propagating antral contraction waves (small arrows) displayed in time intervals of 10 s. Proximal stomach (fundus), pylorus, liver (L), and gallbladder (GB) are indicated (Schwizer and others 2006).

centimeters from the antrum of a human stomach. The tube was connected with a traction force catheter. The forces measured were predominantly from traction on the balloon by the longitudinal vector resulting from circumferential gastric contractions. Cumulative forces on the balloon averaged 6 and 22 N in 30 min to 2 h for the emptying of a liquid and solid meal, respectively. The force per contraction averaged 0.2 N (Vassallo and others 1992; Camillieri and Prather 1994). Kamba and others (2000, 2001) determined the force using a "destructive force dependent release system" (DDRS), which is a press-coated tablet (7 mm in length and about 4 mm in width) with an extremely brittle Teflon outer layer featured by a range of fracture strengths. The DDRS contained a marker drug that was released only when the tablets received a force larger than its predetermined crushing strength. The mechanical destructive forces were determined as 1.50 N under fasting conditions and 1.89 N under fed conditions (Kamba and others 2000, 2001). Marciani and others (2001) used similar approach but with agar gel beads (diameter 1.27 cm) instead of DDRS, and reported a force of 0.65 N exerted by the antral walls of a human stomach in grinding food. The result of Marciani and others (2001) may be more accurate because they used magnetic resonance imaging (MRI) to directly image the breakdown of the agar gel beads in the antrum.

Hydrodynamics of gastric flow and computational simulation

In the GI tract, different hydrodynamic conditions are present, depending on the fasting or the fed state. Fluid motion within the stomach is generated primarily by the gastric wall motion associated with antral contractile activity, pyloric opening, and fundic contractions (Scholz and others 2002; Pal and others 2004). In the fasting state the motility pattern is dominated by a cyclic pattern consisting of 4 phases with duration of approximately 120 min. The fluid movement is rare in phase I but rapid in phase III. It is more regular in the fed state with a continuous movement (Scholz and others 2002).

When food bolus enters the stomach, the breakdown of the bolus is by a process of elution (Marciani and others 2001). Peripheral components of the meal bolus that are closest to the contractile activity are emptied first. Figure 5 shows a typical example of dilution map images of the stomach contents at different times for a high-viscosity polysaccharide meal monitored by EPI. The outer part of the viscous meal was diluted first (coded in red) by gastric and salivary secretions. Then the secretions slowly penetrated toward the core of the meal. The characteristic flow velocity is established by the propagation speed of the antral contraction waves (2 to 3 mm/s) (Bilecen and others 2000; Kwiatek and others 2006); Abrahamsson and others (2005) suggested that the fluid flow is laminar with Reynolds numbers on the order of 0.01 to 30.

Computational modeling has been used to construct flow paths for fluids and particles in the fluid motion, determine fluid forces in the fed stomach, and evaluate the stresses on foods and tablets that cannot be tracked visually (Pal and others 2003, 2004, 2007; Abrahamsson and others 2005; Schulze 2006). With the data of stomach geometry, luminal pressures, and boundary movements from simultaneous MRI and high-resolution manometry, Pal and others (2003, 2004) developed a 2-dimensional computer model of the human stomach with the "lattice-Boltzmann" method. The model demonstrated that antrum contraction waves (ACW) are central to gastric mixing. The strongest fluid motion is around the lumen occlusion, where the retropulsive jet is generated by contractions in the antrum, with jet velocity up to 7.5 mm/s. Food particles receive highest fluid surface shear stresses (100 to 300 dynes/cm^2). On the

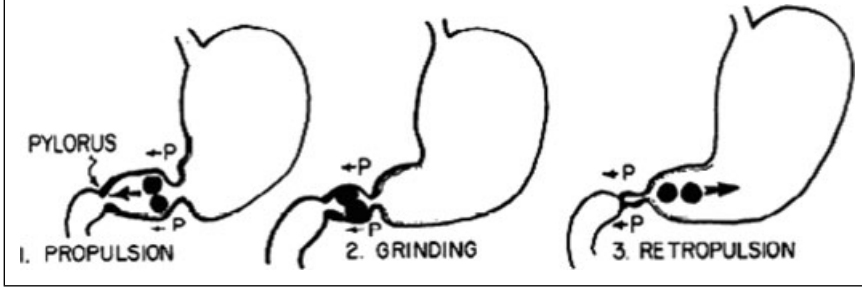

Figure 4—Propulsion, grinding, and retropulsion of solids by peristaltic contractions of distal stomach (Used with permission, Kelly 1980).

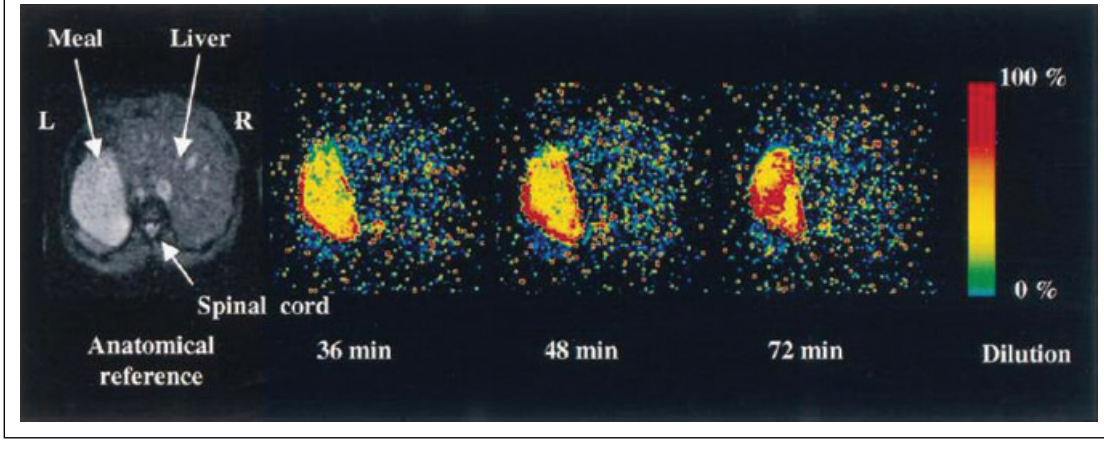

Figure 5—Color-coded dilution maps acquired at different times after a volunteer ingested 500 mL of viscous locust bean gum meal. A transverse EPI image is also shown as an anatomic road map (L, left; R, right) (Used with permission, Marciani and others 2001).

contrary, the fluid motion was very low within the fundus with low shear forces on food particles (< 10 dynes/cm^2). Another pattern of fluid motion identified was flow vortices (or eddies) that circulated particles between successive contraction waves, which may be critical to digestion by producing radial mixing and elution (Figure 6). The relative density of particles was important in breakdown and mixing of food within the stomach due to its strong effect on global particle transport within the stomach. With this model, Pal and others (2007) further discovered a "stomach road," a narrow and short path through the center of the antrum, by which the gastric liquid can move from the fundus to the duodenum within 10 min.

In vivo and *in vitro* experiments are needed to validate computational results. In addition to hydrodynamic flow, the mechanical destructive force, resulting from the grinding or crushing of GI contents and/or friction between food/drug products and the GI wall, is important in disintegrating food and drugs in the stomach (Shameem and others 1995; Kamba and others 2002). This must be incorporated into computational models to accurately simulate the digestion process. Future computations may also need to consider 3-dimensional modeling of gastric flow.

In vitro and *in vivo* Study of Gastric Digestion

In vivo methods to study food disintegration and gastric emptying

In vivo approaches for investigating food disintegration in the GI tract are conducted by a feeding study, and acquiring the digesta samples using naso-gastric and naso-jejunal tube. The fluid digesta samples are aspirated from the stomach and upper small intestine or the terminal ileum (Marciani and others 2000). These samples may be analyzed for size of food particulates and rheological properties such as density and viscosity.

Various instruments and techniques have been developed to study digestive process in the upper GI tract. Those techniques are commonly applied for evaluating gastric motility, accommodation, emptying, and intragastric processing of food. Intubation techniques, scintigraphy, ultrasonography, and MRI have been used to assess gastric disintegration and emptying of food and drugs in clinical and research settings. These techniques are briefly summarized in this section. For further details, readers are referred to related papers (Kim and others 2000; Parkman and others 2004; Schulze 2006).

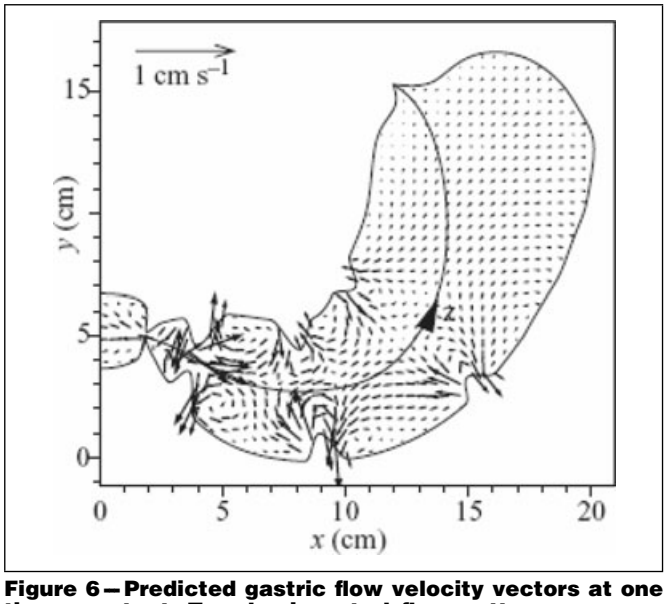

Figure 6—Predicted gastric flow velocity vectors at one time constant. Two basic antral flow patterns are produced by the propagating ACWs, retropulsive jet-like motions in the most highly occluded region, and recirculating eddy flow between pairs of ACWs. The strongest fluid motions are in the antrum (Pal and others 2004).

Intubation techniques, including gastric barostat and intraluminal manometry, are regarded as the "gold standards" for assessing motility of the stomach (De Schepper and others 2004; Kwiatek and others 2006). Gastric barostat uses a balloon to measure proximal stomach accommodation response. The balloon, connected to a computerized pump, is positioned in the proximal stomach to record intraballoon volume at a fixed pressure as a measure of fundic tone. Manometric equipment was developed during the 1970s for detailed study of contractile patterns by measuring intraluminal pressure. The disadvantage of intubation methods is the invasive nature poorly tolerated by patients and possible disturbances of normal physiology and motility patterns induced (Feinle and others 1999; Choe and others 2001; Simonian and others 2004).

Imaging methods provide a noninvasive alternative. The application of scintigraphic methods started in the 1960s and is now considered to be the standard method to measure gastric emptying. Scintigraphy involves using a physiological test meal (solids with/without liquids) labeled with radioactive chemicals such as ^{99m}Tc rhenium sulfide macrocolloids and imaging their transit and dispersion during delivery through GI tract. Analysis of the sequential computer-generated images reveals disintegration and emptying time of the meal. The disadvantage, however, is that it requires administration of relatively high doses of radioisotopes (Feinle and others 1999; Choe and others 2001; Simonian and others 2004). Ultrasonography measures gastric volume or antral cross section. The information is used to estimate the rate of emptying and evaluate antral motility. Ultrasonography involves time-consuming procedures and needs trained operators. Furthermore, it is difficult to measure proximal and distal gastric regions simultaneously (Feinle and others 1999; Choe and others 2001; Simonian and others 2004). MRI uses nuclear magnetic resonance to render images of organs, allowing instantaneous and concurrent assessment of gastric volume responses and emptying and related antral motility with good spatial resolution. Therefore its use has increased rapidly since 1990s (Feinle and others 1999; Choe and others 2001; Simonian and others 2004; Kwiatek and others 2006). Real-time (or echoplanar) MRI has been adapted for rapid sequence scanning which allows monitoring of the movements of the gastroduodenal boundaries and of the luminal contents simultaneously (Figure 5). The results can be used to reveal information of particle size and density, viscosity of gastric contents, and amount of gastric secretions, and to map in 3 dimensions the intragastric distribution of food mass (Marciani and others 2001; Schulze 2006). A limitation for using MRI is the expensive equipment involved. In addition, MRI measurements require patients to be in horizontal body position that may cause differences in intragastric meal distribution and stomach emptying compared to the upright, seated body position (Boulby and others 1997; Jones and others 2006).

Indirect methods such as blood test and breath test are also used for studying gastric emptying and release of drug and bioactive ingredients in the GI tract. These methods are often preferred due to no radioactive exposure or expensive imaging facility. ^{13}C-labeled isotopic acid breath test is gaining special attention as a suitable method for measuring the gastric emptying of solids (Choe and others 2001; Klein 2001; Marciani and others 2001). This method involves introducing ^{13}C into one or more functional groups in a substrate. The functional group is cleaved by specific enzymes in the small intestine, which is further oxidized to CO_2 that is excreted in

breath. Since the rate of solid gastric emptying is the rate-limiting step of the whole process, a test of $^{13}CO_2$ in respiratory CO_2 provides a measure of solid-phase emptying (Parkman and others 2004).

In vitro GI tract models

Compared with *in vivo* study, *in vitro* techniques can save labor and time, reduce cost, and improve accuracy and reproducibility. Another advantage for *in vitro* test is that there is no ethical constraint that often limits human experimentation. A number of *in vitro* GI tract models are currently available for nutrition, toxicology, pharmacology, and safety assessments.

There are 2 types of GI tract models: static and dynamic. Static models do not mimic the physical and physiological processes that occur *in vivo*, such as pH change and peristaltic movements. Physical structure and physicochemical characteristics of food are rarely taken into account in determining *in vitro* food digestion. The simulated gastric digestion often simply involves peptic hydrolysis of homogenized food at pH 1.5 for 1 to 2 h while stirring at 37 °C (Hoebler and others 2002). These models have been used to assess the quantitative release of functional ingredients and nutrients in food and drugs, such as tyrosol in enriched custards (Sanz and Luyten 2006), carotenoids in carrot matrix (Garrett and others 1999; Hedrén and others 2002), antioxidants in wholegrain foods (Nagah and Seal 2005), and isoflavonoids in soy bread (Walsh and others 2003). A recent study involved the static model to evaluate the bioaccessibility of organic pollutants (Dean and Ma 2007).

Compared with a static model, a dynamic GI tract model simulates the physical processing and physiological events that occur *in vivo*, as well as the effects of the food (Moreno 2007). Arnold and Dubois (1983) used a silicone rubber tube (i.d. 19 mm), placed in a peristaltic pump, to produce gastric mixing of food. Molly and others (1993) and De Boever and others (2000) developed a simulator of the human intestinal microbial ecosystem to study the interactions of microbial community in the GI tract. It consisted of 6 computer controlled multichamber reactors simulating the conditions of stomach, duodenum/jejunum, ileum, caecum/ascending colon, transverse colon, and descending colon. This model was used for studying the viability of probiotics (Nollet and others 1997). Hoebler and others (2002) developed a dynamic digestion system in which the pH and pepsin contents were automatically adjusted by pumps under the control of a computer. Similar models were used for studies on ingestion of contaminants from food (Versantvoort and others 2004, 2005) and soil (Oomen and others 2003).

The TNO intestinal model (TIM), developed at TNO Nutrition and Food Research (Zeist, The Netherlands), is a commercial dynamic GI tract model and gaining wide use in pharmacological and food testing for human and animal trials (Souliman and others 2006; Yoo and Chen 2006; Cardot and others 2007; Parada and Aguilera 2007). It is designed to mimic the human physiological conditions in the stomach and small intestine, including simulation of pH changes, temperature, peristaltic movements, secretion of digestion enzymes, bile and pancreatic juices, and absorption of digested products. TIM consists of 4 serial compartments (Figure 7) simulating the stomach, duodenum, jejunum, and ileum. In each compartment, water at 37 °C circulates in glass jackets around flexible walls. The flexible walls are compressed and relaxed by changing the water pressure which enables mixing of chyme. The chyme is transited through gastric and intestinal compartments by opening or closing the peristaltic valves that connect the compartments. The volume of compartments, pH, enzymes, and salts are monitored and continuously controlled by computer. TIM has been used to evaluate bioaccessibility of folate in fortified milk (Verwei and others 2003), absorption of mutagenics in foods (Krul and others 2000), viability of probiotic intake (Mattila Sandholm and others 1999; Krul and others 2001), and phenolic compound release from a food matrix such as orange juice, strawberries, and strawberry jam (Gil-Izquierdo and others 2002). It has been also used to assess drug dissolution and release under various physiological GI conditions and to study drug–food interactions (Blanquet and others 2004; Souliman and others 2006, 2007).

Despite its wide suitability, TIM is not a quality control tool due to its complexity (Cardot and others 2007). The model cannot quantitatively reproduce the fluid mechanics and the mechanical forces encountered *in vivo* in the human GI tract. Furthermore, it is difficult to mathematically model the digestion process in the TIM for predicting the fate of food or other ingested materials (Yoo and Chen 2006).

A well-designed the *in vitro* model may provide accurate estimation of the *in vivo* situation. For example, studies have shown that a static model is capable of distinguishing between iron availabilities of complex mixture of foods, and the magnitude of the responses resembles those found in human trials (Schricker and others 1981). However, the correlation is significantly dependent on the model design and physical and chemical properties of the materials tested. For example, TIM model simulates absorption of food components by dialysis, which enables a satisfactory prediction for the fate of water-soluble compounds smaller than 5000 Da, but not for compounds with other absorption mechanisms (Krul and others 2000). Therefore, quantitative validation of an *in vitro* digestion model for the *in vivo* situation is recommended before the *in vitro* model is used (Versantvoort and others 2004).

USP dissolution testing

Although no standard has been published specifically for the disintegration of foods in GI tract, the United States Pharmacopeia

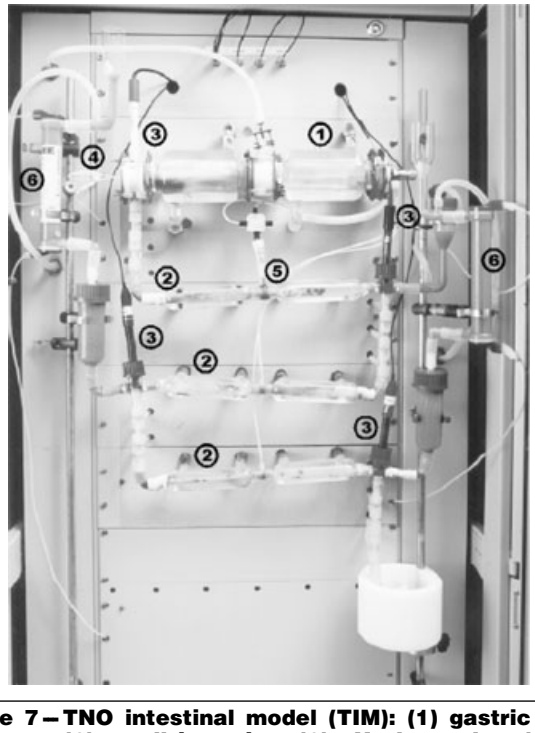

Figure 7—TNO intestinal model (TIM): (1) gastric compartment; (2) small intestine; (3) pH electrodes; (4) secretion of lipases and pepsin; (5) secretion of pancreatic juice and bile; and (6) hollow fiber membranes simulating the absorption of digested products (Krul 2003).

(USP) has published disintegration and dissolution standards for evaluating drug tablets and capsules, and nutritional dietary supplements (vitamins, minerals, herbs) (Yetley 2007). These standards assume that *in vitro* acid solubility is a surrogate for *in vivo* absorption. USP disintegration and dissolution tests are widely used in the characterization of drugs and in quality control of drug dosage forms and nutritional supplements. The information on principles and applications of USP test may be useful in developing standards for *in vitro* evaluation of food disintegration and dissolution in GI tract.

According to USP, dissolution refers to the process by which the active ingredient is dissolved into a liquid assay medium, and the result provides the approximate time required for full solubilization of the drug under the test conditions (Yetley 2007). It is monitored by chemical analysis. Four basic types of dissolution apparatus are specified by the USP and recommended in the FDA guidance. Apparatus 1 is also called rotating basket, using 40-mesh wire basket rotated in a dissolution medium at a constant speed between 25 and 150 rpm. Apparatus 2, or the paddle method (Figure 8), is similar to apparatus 1 except that the rotating basket is substituted with a paddle. Apparatus 3, or a reciprocating cylinder, involves enclosing the dosage form in a transparent cylinder that is reciprocated up and down in the medium contained by a glass tube in a water bath. In apparatus 4, the dissolution medium is continuously pumped through a flow-through cell that contains the dosage form and is immersed in a water bath. The first 2 methods are preferred and commonly used (FIP 1996).

Main factors that influence release of drug ingredients include pH, surfactant, bile, movement, ionic strength, buffer capacity, enzymes, and the presence of foods (Dressman and Reppas 2000; Cardot and others 2007). The dissolution medium can be varied to suit different test purposes. An aqueous dissolution medium composed of 0.1 N HCl (or pH 1.2) is often employed to simulate gastric medium (FIP 1996). The commonly used agitation speed is 50 to 100 rpm for basket method and 25 to 75 rpm for paddle method (FIP 1996; Emami 2006). The dissolution curves are expressed as the percentage dissolved compared with time. Based on this curve, various parameters such as the time to achieve 10%, 50%, and 90% dissolved and the dissolution rate can be calculated.

The USP disintegration apparatus consists of a basket rack holding 6 plastic tubes open at the top and bottom. The bottom is covered with a 10-mesh screen. The rack is immersed in a suitable liquid (for example, simulated gastric fluid or 0.1N HCl) at 37 °C. It moves up and down at a specified rate. The time required for full disintegration is recorded for each individual tube. This process is monitored visually. The USP definition of drug disintegration is "that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core" (Epstein and Ragi 2004).

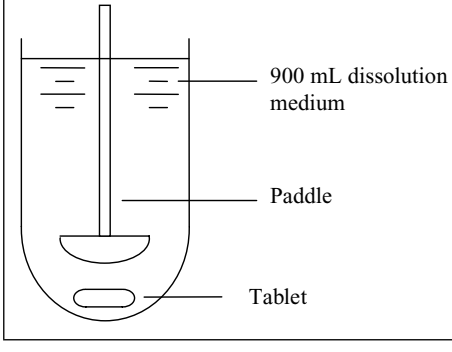

Figure 8—USP apparatus 2 (paddle method).

Researchers have tried to correlate *in vivo* results with those from USP dissolution testing, and the correlation seems to be possible to establish in some cases. For example, Abrahamsson and others (1998) showed that a test medium with an ionic strength of 0.14 was able to provide physiologically relevant conditions, and the mechanical stress exerted by the GI motility on the hydrophilic tablets corresponds to paddle stirring rates around 150 rpm in the USP apparatus. Scholz and others (2003) documented that agitation with paddle speeds of 75 rpm and 125 rpm are a good simulation of the hydrodynamics *in vivo* for "fasted" and "fed" states, respectively. However, the estimation of *in vivo* drug release from *in vitro* dissolution tests often ends in failure. For example, *in vivo* drug release of hydrogel-type tablets was much faster than that from *in vitro* dissolution tests (Shameem and others 1995). One major reason for the lack of *in vivo–in vitro* correlation is the deficiency of mechanical stress in the *in vitro* test. In addition to hydrodynamic flow, mechanical impact or mechanical destructive force is crucial in digestion process that arises from grinding or crushing of GI contents and/or friction between drug products and the GI wall (Shameem and others 1995). This type of mechanical force is scarcely involved in the paddle method (Aoki and others 1994; Souliman and others 2007). This is also true for USP disintegration testing. Kamba and others (2003) reported that the mechanical destructive force in the disintegration test is much smaller than that in the human stomach. To solve this problem, Aoki and others (1993, 1994) proposed a paddle-beads method in which polystyrene beads (5 mm in diameter) were introduced into the liquid medium to create a friction/impact force on drug tablets in test. With paddle rotation set at 25 rpm in 250 mL of liquid medium containing 2500 beads, the profile of *in vitro* release using the paddle-beads method was determined to be similar to that of *in vivo* release in the fasted condition in dogs (Aoki and others 1993).

In vitro–in vivo correlation (IVIVC)

As stated above, due to the complexity of the GI tract *in vivo*, *in vitro* tests are not always reliable in predicting the behavior of food or a drug dosage for *in vivo*. Thus the need for a tool to reliably correlate *in vitro* and *in vivo* drug release data remains a high priority. In recent years, the concept of the IVIVC for pharmaceutical dosage has attracted major focus and application in the pharmaceutical research (Emami 2006; Cardot and others 2007).

According to guidance provided by FDA regarding IVIVC (FDA 1997), 3 main levels can be defined, levels A, B, and C. The correlation level is determined based on the ability of *in vitro* test to reflect the *in vivo* data after administration of the given dosage form. For a drug test, the *in vivo* data are derived from the plasma concentration curve. To demonstrate a correlation, the fraction absorbed *in vivo* is plotted against the fraction released *in vitro*. Level A correlation is defined when a linear relationship exists between the 2 sets of data with a slope of 1; that is, curves are superimposable. Level A correlation represents a point-to-point relationship between *in vitro* dissolution and *in vivo* dissolution (input/absorption rate). It is the most informative and useful from a regulatory perspective. In level B correlation, the mean *in vivo* dissolution or mean residence time is compared to the mean *in vitro* dissolution time by using statistical moment analytical methods. This type of correlation uses all of the *in vitro* and *in vivo* data; thus, it is not considered a point-to-point correlation. Level C correlation describes a relationship between the amount of drug dissolved (for example, percent dissolved at 1 h) at 1 time point and

1 pharmacokinetic parameter (for example, time to peak concentration). It is considered to have the lowest correlation level, because it does not reflect the complete shape of the plasma concentration time curve.

Souliman and others (2006, 2007) compared the *in vitro* and *in vivo* dissolution of acetaminophen and theophylline hydrophilic matrix tablets. *In vitro* methods included the TIM and USP paddle methods. *In vivo* test was conducted by measuring plasma concentrations. The potentiality of each method was evaluated by establishing *in vitro*/*in vivo* correlation. For TIM, a level A *in vitro*/*in vivo* correlation was established, with correlation coefficients of 0.9128 and 0.9984 for the dissolution of acetaminophen tablets in the fasted and fed states, respectively. However, level A correlation was not observed for the USP paddle method (Souliman and others 2006, 2007). The high efficacy of TIM in predicting *in vivo* drug tablets behavior is attributed to its ability to simulate the peristaltic movements and the contraction force in the GI tract, as well as the proper use of enzymes and appropriate adjustment of pH (Souliman and others 2006, 2007).

Gastric Digestion and Emptying of Foods

Mechanism of gastric emptying of solid foods: biphasic nature

Gastric emptying results from the net effects of propulsive forces within the stomach and the resistance to flow offered by the narrowed gastroduodenal junction. The emptying rate is determined by the balance between driving and resistive forces (Vassallo and others 1992; Schulze 2006). Liquids, digestible solids, and indigestible solids are emptied with different mechanisms (Stotzer and Abrahamsson 2000). Liquid and semiliquid contents, as well as particles with a size of 1 to 2 mm, are emptied from the stomach into the duodenum during fed motility, whereas the contents of size $>$ 1 to 2 mm are emptied during fasting motility (Hellström and others 2006). The proximal stomach has a major role in gastric emptying of liquids and the distal stomach a major role in gastric emptying of solids (Kelly 1980; Vassallo and others 1992).

After ingestion, liquids are rapidly distributed throughout the entire stomach. Emptying of liquids depends mainly on fundic pressure, through the "pressure pump" mechanism controlled by pyloric opening where the gastroduodenal pressure gradient is the driving force (Indireshkumar and others 2000; Stotzer and Abrahamsson 2000). Liquid meals empty from the stomach according to 1st-order kinetics; that is, the speed is directly proportional to the volume present in the stomach (Figure 9). It has an initial gastric emptying rate after ingestion of a meal, up to 10 to 40 mL/min, followed by a slower emptying rate of 2 to 4 mL/min. The halftime, $t_{1/2}$, indicating when 50% ingested meal is emptied, ranges from 10 to 60 min (Fisher and others 1982; Versantvoort and others 2004; Hellström and others 2006).

Ingested solids are stored initially in the proximal stomach and move gradually into the distal stomach. The propulsive contractions of the antral pump are the most important mechanisms underlying gastric emptying of solid food, where trituration is a rate-limiting step (Collins and others 1996; Cardoso-Júnior and others 2007). In the gastric antrum, mechanical (antral contractions) and chemical (acid, pepsin, and so on) factors work in coordination to grind and dissociate the solid particles. Solids are ground to particles of a size less than 1 to 2 mm before they are allowed to go through the pyloric opening. Indigestible material must wait for the interdigestive phase when the phase III contraction of the migrating motor complex empties the stomach (Poitras and others 1997; Stotzer and Abrahamsson 2000). The gastric emptying rate of solids, as indicated by the fraction of meal retention in the stomach compared with time, shows a biphasic pattern: a lag phase during which little emptying occurs, followed by a linear emptying phase during which solid particles empty from the stomach by mainly zero-order kinetics, that is, independent of gastric volume (Figure 9) (Siegel and others 1988; Hellström and others 2006; Schulze 2006). The stomach empties solids completely over approximately 3 to 4 h (Versantvoort and others 2004).

Since the early 1980s, scintigraphic imaging has been commonly used to evaluate gastric emptying rate. Various models and mathematical curves have been proposed for evaluation of gastric emptying rate, as indicated by fraction of food retention compared with time. With scintigraphic data, the food retention is assessed by the radioactivity remaining in the stomach. Two of the most popular models are Elashoff's power exponential curve (Elashoff and others 1982) and Siegel's modified power exponential curve (Siegel and others 1988).

Elashoff's power exponential equation is as follows (Marshall and others 2005):

$$y(t) = 2^{-(t/T_{1/2})^{\beta}} \tag{1}$$

where $y(t)$ is the fractional meal retention at time t in minutes, $T_{1/2}$ is the time required for the initial radioactivity to be reduced by half, and β is a constant that determines the shape of the curve. Siegel and others (1988) further modified Elashoff's model to account for the lag phase:

$$y(t) = 1 - (1 - e^{-kt})^{\beta} \tag{2}$$

where k is the gastric emptying rate per minute, and β is the extrapolated y-intercept from the terminal portion of the curve. A value of $\beta > 1.0$ indicates an initial delay in emptying as for the solid foods, whereas a value of $\beta < 1.0$ indicates an initial rapid emptying as for liquid foods (Siegel and others 1988). The half-time ($t_{1/2}$) can be calculated using $y(t) = 0.5$ and solving for t,

$$t_{1/2} = (-1/k) \cdot \ln(1 - 0.5^{1/\beta}) \tag{3}$$

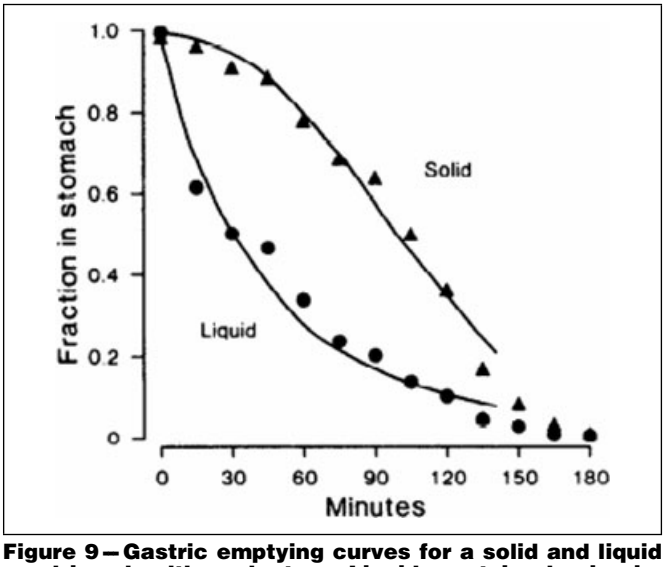

Figure 9—Gastric emptying curves for a solid and liquid meal in a healthy volunteer. Liquid emptying begins instantly in an exponential fashion, whereas the linear solid emptying begins after the lag phase. The emptying data is fitted with curves by power exponential model (Eq. 1). (Used with permission, Camilleri and others 1985).

For solid foods, lag phase was defined as the time taken to achieve maximum rate of gastric emptying after ingestion of a test meal. This is usually correlated with the time when 90% of the test meal remained in the stomach. Despite some of the opposing arguments, it is commonly accepted that lag phase primarily reflects the time needed by the distal stomach to reduce ingested solid food into particles small enough to pass through the pylorus (Siegel and others 1988; Urbain and others 1989). Lag phase time (t_{lag}) can be calculated by assuming that the 2nd derivative of the function is equal to zero,

$$t_{lag} = \frac{\ln \beta}{k} \quad (4)$$

Although the modified power exponential model is thought to be the best to fit experimental data and is commonly used to evaluate stomach emptying rate, the lag period calculated by Eq. 4 has been noted for its overestimation (Ziessman and others 1996; Hellström and others 2006).

Gastric emptying is regulated by both gastric factors and, to a greater extent, duodenal factors. Gastric factors include the food volume, fluid viscosity, caloric content, acidity, and food physical properties such as texture and density (Arora and others 2005). Duodenal gastric feedback is the major control mechanism for gastric emptying. The duodenum contains receptors that respond to distention, the presence of acid, carbohydrate, fat, and protein digestion products, and osmolarity differences from that of plasma (Versantvoort and others 2004). Chemical composition of the meal and the physical nature of the food remain crucial in regulating emptying rate. This information, important for understanding relationships between the physical and chemical properties of foods and digestion, is introduced in the following sections.

Biological factors such as age, body mass index, hormonal factor, gender, the blood glucose level, posture, stress and depression, and diseased states also influence gastric emptying (Amidon and others 1991; Darwiche and others 2003; Arora and others 2005; Hellström and others 2006). For example, gastric emptying is slower in elders and females. This could be related to the weaker antrum contractions in elders and women, because emptying rate is inversely correlated with the rate of antrum contractions (Houghton and others 1988). Emptying rate increases under stress and decreases in depression (Amidon and others 1991; Arora and others 2005). Fluids ingested at body temperature are emptied faster than colder or warmer fluids (Arora and others 2005). An increase in the osmolarity of the stomach contents decreases gastric emptying rate (Versantvoort and others 2004). The influence of biological factors on gastric emptying is not directly related to the theme of this review; therefore, it is not discussed here.

Influence of food caloric content, macronutrients, and volume on gastric emptying

Gastric emptying is so controlled that about 2 to 4 kcal/min (8.4 to 16.8 kJ/min) caloric content is delivered to the duodenum through a negative feedback mechanism mediated by the duodenal receptors. Meals with similar energy content are emptied from the stomach at similar rates (Faas and others 2002; Gentilcore and others 2006; Hellström and others 2006). In this context, meal calories, compositions, and size are important for gastric emptying. Meals of larger weight and kcal content are associated with longer emptying time for both solids and liquids (Horowitz and others 1986; Hadi and others 2002). Liquids with a calorie density of 1 kcal/mL are emptied at about 2 to 2.5 mL/min, whereas liquids of 0.2 kcal/mL are emptied at about 10 mL/min (Dressman and others 1998). The rate of energy delivery is faster with the larger meal. For example, a 150-mL meal containing 10% dextrose combined with 400 g ground beef was delivered at 4.8 kcal/min, whereas that with 100 g beef was delivered at only 2.5 kcal/min. Meanwhile, a delay in the lag phase of emptying was observed: 56 min for the large meal and 31 min for the small meal, respectively (Collins and others 1996). Moore and others (1984) determined that 900 g lettuce and water meals adjusted to either 68, 208, or 633 kcal with added salad are emptied at 3.18, 2.56, and 1.46 grams/min, corresponding to 0.48, 1.18, and 2.04 kcal/min, respectively. Christian and others (1980) showed that the average $t_{1/2}$ for emptying meals consisting of meats, vegetables, and beverages were 277, 146, and 77 min, respectively, for 1692, 900, and 300 g meals. The $t_{1/2}$ for the liquid part of these meals was 178, 81, and 38 min, respectively.

Among the major components of foods, fat is emptied more slowly than carbohydrates and proteins. Emptying 4 g of fat emulsion takes the same time as for a solution of 9 g of carbohydrate or protein. This is primarily because of its high caloric density, roughly 9 kcal/g in fat and 4 kcal/g in carbohydrate or protein (Versantvoort and others 2004; Gentilcore and others 2006). In addition, density difference causes phase separation of chyme in stomach, leading to the layering of fat above water that may also contribute to the longer emptying time of fat (Versantvoort and others 2004). Another possible reason is that fat absorption rate in the intestine is relatively slower that delays emptying speed (Gentilcore and others 2006).

Different sugars empty from the stomach at different rates. Lavin and others (2002) showed that the $t_{1/2}$ values for 575 mL lemon-flavored drink of sucrose or maltose (125 g + 450 mL water + 50 mL lemon juice, 516 kcal) are 86 ± 5 min and 115 ± 2 min, respectively, whereas that for an unsweetened 575 mL lemon-flavored drink (525 mL water + 50 mL lemon juice, 16 kcal) was only 39 ± 2 min.

Complex interactions occur when different types of solids and liquids are consumed simultaneously (Collins and others 1996). For example, distinct $t_{1/2}$ were observed for 10 mm chicken liver when ingested with 2 different meals: 117 min for a meal of 200 mL of water + 213 g of beef stew + 52 g of chicken liver, compared with 82 min for a meal of 200 mL of water + 75 g of noodles + 30 g of chicken liver (Moore and others 1981). Eggs and liver cubes have different emptying rates when they were ingested individually, but were emptied at a similar rate when ingested together (Poitras and others 1997). Ingested solid and liquid foods affect each other. Simultaneous ingestion of solids slowed significantly the gastric emptying rate of the liquid component (Fisher and others 1982). The liquid composition also affects solid emptying. Houghton and others (1988) showed that when the liquid component of the meal changed from normal saline to 25% dextrose, the lag period for solid emptying increased from 40 to 87 min. Meanwhile, liquid emptying $t_{1/2}$ increased from a median of 8 to 40 min. However, the slope of solid emptying did not change, implying that the rate of coordinated contractions involving the antrum did not alter during the solid emptying period (Houghton and others 1988).

Influence of food viscosity on gastric emptying

Increasing the viscosity of liquid meals delays gastric emptying and increases satiety (Ehrlein and Pröve 1982; Benini and others 1995). An experiment on dogs showed that $t_{1/2}$ was 4.5 ± 2.2 min with a low viscosity liquid meal (10^{-3} Pa.s), 28.9 ± 9.5 min with a test meal of medium viscosity (10^{2} Pa.s), and 43 ± 11.8 min with a test meal of high viscosity (10^{3} Pa.s) (Ehrlein and Pröve 1982). Studies have shown that addition of soluble fibers such as pectin (Di Lorenzo and others 1988), guar gum (Blackburn and Johnson 1981; Leclère and others 1994), and locust bean gum (Marciani and

others 2001; Darwiche and others 2003) reduces the gastric emptying rate, delays absorption, reduces the plasma glucose response, and slows down the return of hunger. For this reason, soluble fibers have been combined in diet for treating pathological conditions such as obesity, hypercholesterolemia, and diabetes.

The mechanisms governing delayed stomach emptying with increased viscosity of meal are thought to be related to the negative feedback from the intestine when fiber arrives in the distal ileum or in the colon (the "ileal brake") (Darwiche and others 2003). It may be also related to the greater resistance of fiber containing food to the intragastric movement of the meal toward antrum and grinding action of the antrum (Benini and others 1995). However, despite an increase in the apparent viscosity of the gastric contents after ingestion of a high viscosity meal (Blackburn and Johnson 1981), the increase in the chyme viscosity is not proportional to the meal viscosity. A rapid intragastric dilution in the stomach occurs after a high viscosity meal is ingested to reduce the meal viscosity and minimize delay in gastric emptying (Meyer and Doty 1988; Marciani and others 2000). This may partly explain the much smaller change in emptying rates compared to the increase in viscosity in the meal. Marciani and others (2000) showed that 1000-fold viscosity variation between meals caused changes in emptying rates by a factor of only 1.3. Guerin and others (2001) studied the influence of meal viscosity on chyme and emptying on conscious pigs, and found that the reduced emptying rate is more associated with changes in intragastric distribution of the meal rather than meal viscosity. They concluded that viscosity of the gastric contents is a better predictor of emptying than the viscosity of the meal. Furthermore, gastric emptying is not only directly related to gastric digesta viscosity but it also depends on the type of dietary fiber (Guerin and others 2001).

The effect of dietary fiber on the gastric emptying rate of solids is controversial. Although different authors have reported a delayed emptying by the fibers added manually (Di Lorenzo and others 1988) or naturally present in food (Benini and others 1995), accelerated gastric emptying was also reported. Meyer and others (1986) documented that the addition of guar gum significantly increased the emptying of 3.2-mm Teflon spheres in a meal consisted of steak and saline. They also observed an increased passage of large, poorly digestible pieces of foods through pylorus: the size of food particles emptied from the stomach increased from < 1 mm to 1 to 4 mm, leading to a reduced absorption in intestine. This phenomenon could be related to the viscosity-induced change in hydrodynamic factors that disrupted gastric sieving (Meyer and Doty 1988).

Influence of physical properties of food on gastric emptying

During gastric digestion, solid foods are ground down to 1 to 2 mm size by the action of gastric peristalsis before being discharged to the duodenum. The physical properties such as size, density, texture, and microstructure of the food are important in determining how easily it can be fragmented in the stomach. Food particles with large size and density need more time for size reduction in the antrum, consequently requiring long time for emptying. The $t_{1/2}$ was 70 ± 10 min for the 0.25 mm chicken liver and 117 ± 19 min for the 10 mm liver particles (Moore and others 1981). Spheres with specific gravity greater than 1 or less than 1 may sink or float out of the central moving stream in the stomach; both are emptied more slowly than spheres of the same size with a specific gravity of 1 (Meyer and others 1985). This principle has been used in the design of floating dosage form, which has a density less than that of the gastric fluids and therefore can be retained in the stomach for a prolonged period (Arora and others 2005).

Hardness of solids affects stomach-emptying rates. Soft particles emptied significantly faster than hard ones. When noodle and liver are ingested simultaneously, noodle was emptied faster (52 ± 8 compared with 82 ± 5 in $t_{1/2}$) (Moore and others 1981). Another study showed a longer $t_{1/2}$ for chicken liver than egg (Siegel and others 1988). Based on this fact, Poitras and others (1997) proposed using liver rather than egg as a radiolabeled tracer in scintigraphy to improve the sensitivity for detection of gastroparesis.

Contrary to intuition, consistency of foods may not make significant difference on emptying. Mashed potato was found to empty from the stomach at a similar rate with meals of a more particulate consistency (rice, hamburger meal), although it did not require trituration in stomach as a homogeneous meal (Faas and others 2002). This may be due to a longer period of time needed for gastric secretions to penetrate and liquefy the meal with denser consistency (Marciani and others 2001; Faas and others 2002).

Food processing affecting digestion

Food processing (during manufacturing or cooking) modifies physical and chemical properties of food, and thus may influence the release and uptake of nutrients from the food matrix. Comminution reduces food size, which significantly improves gastric emptying rates and nutrient absorption (Bjorck and others 1994; Pera and others 2002). The lag phase and half emptying time ($t_{1/2}$) were significantly shorter for the homogenized egg meal than for the 2.5 mm and 5.0 mm cubed egg particles, with the lag phase 29 ± 19 min compared with 55 ± 26 and 64 ± 24 min, and the $t_{1/2}$ 71 ± 30 min compared with 91 ± 26 and 104 ± 30 min, respectively (Urbain and others 1989). An *in vitro* digestion study showed that 3% of the carotenoid content was released from raw carrots in pieces, whereas 21% was released from the homogenized (pulped) carrots (Hedrén and others 2002).

Thermal processing can significantly affect digestion of protein (Ruales and Nair 1994), starch (Lee and others 2005), fat (Benini and others 1994), and vitamins (Yeum and Russell 2002). Heat treatment significantly improves bioavailability of carotenoid and lycopene in vegetables (Yeum and Russell 2002). Fried meal showed significantly delayed emptying time (317.1 ± 24.12 compared with 226.7 ± 18.4 min) and caused a longer persistence of satiety and epigastric fullness in human trials, which could be attributed to the effect of thermal oxidation on fat absorption (Benini and others 1994). Cooking improves bioavailability of starch by splitting the starch granules and increasing the availability of the starch to amylase (Brand and others 1985). Lee and others (2005) studied the effects of various cooking methods on rice texture, microstructure, and digestion in rats. Cooking methods studied included microwave oven, electric cooker, autoclaving, and a stone pot. Scanning electronic microscopy showed a more compact structure in the samples heated by microwave and electric cooker compared to those treated in an autoclave or stone pot, corresponding to a higher firmness in the samples heated by microwave and electric cooker. Cooking increased pasting temperatures and decreased peak viscosity. The starch hydrolysis rates of cooked rice samples increased with an increase in gelatinization. Holm and others (1989) also documented that incompletely gelatinized starch products were digested more slowly *in vitro* and elicited lower glucose responses in rats compared with completely gelatinized samples.

Summary and Recommendations for Future Research

In the human stomach, mechanical and chemical actions work in coordination to break down solid foods into particles of 1 to

2 mm size before being emptied into the intestine. The rate of food disintegration in stomach is a key factor influencing emptying rate and subsequently affecting absorption of nutrients in the intestine. It is reported that faster disintegration and emptying of drug tablets is responsible for the faster absorption of drug ingredients in the intestine (Kelly and others 2004). Studies in medicine, pharmacy, and nutrition have demonstrated that food disintegration in stomach is a complex process involving numerous variables, including particle size, meal volume, calories and composition of the meal, viscosity, and physical properties such as texture and structure. These and related factors, decide the time taken for food to be disintegrated and emptied from stomach, and significantly affect the efficiency of systemic delivery of the food component for absorption.

Nutrient bioavailability is gaining considerable attention in food technology. To develop structured foods and develop a strategy for controlled release of food nutrients at desired sites in the GI tract, it is essential to understand the kinetics of food disintegration and predict the digestion and subsequent metabolism. The biochemical, physiological, and physicochemical parameters that influence these processes need to be understood. This understanding will not only benefit food-processing industry in developing proper food structures for health purposes, but also help medical, pharmaceutical, and nutritional researchers in seeking proper approaches to modulate gastric emptying for optimizing glycemic control.

Past studies on food digestion in stomach involved using scintigraphy or MRI methods to investigate the intragastric movement and distribution of bulk foods and its delivery from the stomach to intestine. However, information is scarce on the influence of hydrodynamic and mechanical forces present in the stomach on food disintegration, as well as the changes of rheological properties of gastric juice and the hydrodynamics of the fluid with ingested meal and its implications on food digestion. How the food material properties such as texture and microstructure affect the gastric disintegration kinetic is rarely studied. Sporadic research has been conducted on the effect of food processing on food digestion and glucose response, but in-depth investigation on the relationships between food processing and the resultant physical and chemical properties of foods, and subsequently their disintegration performance in the GI tract, is lacking.

To develop the next generation of foods for health that provide targeted delivery of nutrients in the GI tract, a combined understanding of materials science, physical chemistry, and biophysics is needed, together with knowledge of how the processing of a food material affects its structure (Norton and others 2007). *In vitro* digestion models need to be developed to enable detailed investigations of food disintegration kinetic as related to the influences of hydrodynamic and mechanical contraction forces that are present *in vivo*. The disintegration kinetic and governing mechanisms vary for different types of foods such as meats, baked foods, vegetables, and nuts. Studies are needed to explore the relationships between food texture, microstructure, and chemical properties and the digestion properties such as disintegration rate and gastric emptying rate. Furthermore, studies are necessary to understand the changes in food ingredients such as protein, carbohydrates, and lipids during food processing and the role of these changes on food digestion. The rheological properties of gastric juice, intragastric fluid motion, and hydrodynamics significantly affect food digestion. This may also be studied with the help of computational simulations. Research in these areas should contribute to the development of innovative processing methods for optimal delivery of nutrients in the GI tract.

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