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Physiological Parameters for Oral Delivery and *In vitro* Testing

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Abstract

Pharmaceutical solid oral dosage forms must undergo dissolution in the intestinal fluids of the gastrointestinal tract before they can be absorbed and reach the systemic circulation. Therefore, dissolution is a critical part of the drug-delivery process. The rate and extent of drug dissolution and absorption depend on the characteristics of the active ingredient as well as properties of the dosage form. Just as importantly, characteristics of the physiological environment such as buffer species, pH, bile salts, gastric emptying rate, intestinal motility, and hydrodynamics can significantly impact dissolution and absorption. While significant progress has been made since 1970 when the first compendial dissolution test was introduced (USP Apparatus 1), current dissolution testing does not take full advantage of the extensive physiologic information that is available. For quality control purposes, where the question is one of lot-to-lot consistency in performance, using nonphysiologic test conditions that match drug and dosage form properties with practical dissolution media and apparatus may be appropriate. However, where *in vitro – in vivo* correlations are desired, it is logical to consider and utilize knowledge of the *in vivo* condition. This publication critically reviews the literature that is relevant to oral human drug delivery. Physiologically relevant information must serve as a basis for the design of dissolution test methods and systems that are more representative of the human condition. As *in vitro* methods advance in their physiological relevance, better *in vitro* - *in vivo* correlations will be possible. This will, in turn, lead to *in vitro* systems that can be utilized to more effectively design dosage forms that have improved and more consistent oral bioperformance.

Keywords

dissolution; absorption; physiologic; physiological; absorption; gastrointestinal; bioperformance; oral drug delivery; physicochemical properties

Introduction

Pharmaceutical solid oral dosage forms directed to the systemic circulation must dissolve in the intestinal fluids of the gastrointestinal (GI) tract prior to absorption, making dissolution vital to drug delivery. Pharmaceutical scientists must understand dissolution to efficiently develop robust dosage forms and ensure that drug products consistently meet critical performance criteria. The rate and extent of drug dissolution and absorption depend on characteristics of the active ingredient such as pK_a, crystal form, and solubility, as well as properties of the dosage form[1]. Just as importantly, characteristics of the physiological environment such as buffer species, pH, bile salts, gastric emptying rate, intestinal motility, hydrodynamics, and shear rates significantly impact dissolution and absorption[2].

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To understand the complicated process of *in vivo* drug dissolution, scientists have attempted to replicate it using a variety of *in vitro* test methods. Numerous methodologies have been developed that are routinely used for quality control purposes (e.g., USP tests) and as tools to understand the effects of formulation and processing changes[3]. While these methodologies have existed for many years and have been used extensively, none accurately reflect *in vivo* conditions. Conventional USP testing methods employ simple, non-physiologic buffers (e.g., phosphate, acetate, maleate) and hydrodynamic conditions (e.g., single-chambered glass vessels) that do not accurately reflect dynamic *in vivo* conditions. To bridge the gap between *in vitro* and *in vivo* dissolution and absorption, the Biopharmaceutics Classification System (BCS) provides some guidance for predicting *in vivo* performance based on a drug's solubility, permeability, and *in vitro* testing results[4]. The BCS has had a significant effect on the regulatory environment as the FDA and WHO consider biowaivers for some drugs, particularly those considered to be BCS Class 1 (high solubility, high permeability) and BCS Class III (high solubility, low permeability)[5].

While significant progress has been made since 1970, when the first compendial dissolution test was introduced (USP Apparatus 1), current dissolution testing does not take full advantage of the extensive physiologic information that is available. For quality control purposes, where the question is one of lot-to-lot consistency in performance, utilizing nonphysiologic test conditions that match drug and dosage form properties with practical dissolution media and apparatus may be appropriate. However, where *in vitro – in vivo* correlations (IVIVCs) are desired, it is logical to consider and utilize our knowledge of the *in vivo* condition. Strides have been made in making dissolution testing methods more biologically based. Dressman et al. developed several biorelevant dissolution media designed to better reflect compositions and physicochemical characteristics of the fasted and fed states in the stomach and small intestine[6]. In addition, several authors have developed dissolution apparatuses that better capture aspects of the physiological environment compared to USP tests[7–9].

Several good reviews of human GI physiology are available[2,10–11] but none provide a comprehensive review of the physiological parameters that influence oral absorption in the context of dosage form performance and drug dissolution. The focus of this publication is to critically review the literature that is relevant to oral human drug delivery. This physiologically relevant information should serve as a basis for the design of dissolution test methods and systems that are more representative of the human gastrointestinal tract. As *in vitro* methods advance in their physiological relevance, better *in vitro - in vivo* correlations will be possible, leading to improved oral bioperformance of dosage forms.

Factors Affecting Dissolution and Absorption

Absorption is what ultimately carries orally administered drugs into the intestinal membrane to be transferred to the blood stream. However, the drug must dissolve before absorption can occur or the drug can act locally in the GI tract. Therefore, it is important to have a fundamental understanding of the key drug properties affecting both dissolution and absorption. These principles have taken a variety of mathematical forms over the years. According to Amidon et al., for example, the fraction of drug absorbed is a function of drug solubility, dose, and GI permeability[4]. According to Equation 1, the flux of drug across the intestinal wall, J_w, is dependent on the intestinal wall permeability, P_w (an effective permeability), and the concentration of drug at the wall, C_w. The equation applies to each point along the membrane, assumes that each parameter is dependent upon time and position, and assumes the concentration of drug in the epithelial cell to essentially equal to zero. Assuming no luminal reactions, the absorption rate is given by Equation 2, where A is

the area available for absorption (i.e., membrane surface in contact with the drug) and m is mass.

$$J_w = P_w \cdot C_w \quad \text{(Eq. 1)}$$

$$\text{Absorption Rate} = \frac{dm}{dt} = \int\int_A P_w C_w dA \quad \text{(Eq. 2)}$$

Factors that affect dissolution can be understood by examining the simple Noyes-Whitney equation, which describes the mass of drug dissolving as a function of time. The equation, for dissolution from a planar surface, is given in Equation 3, where M is mass, D is drug diffusion coefficient, A is drug surface area available for dissolution, h is empirical thickness of the hydrodynamic boundary layer, C_s is the solubility at the solid liquid interface, and C_b is the bulk drug concentration[12].

$$\text{Dissolution Rate} = \frac{dM}{dt} = -\frac{DA}{h}(C_s - C_b) \quad \text{(Eq. 3)}$$

Each of the parameters in Equation 2, describing absorption, and Equation 3, describing dissolution, is influenced by properties of the drug substance, drug product, and GI tract.

From the above description it is clear that *in vivo* dissolution and absorption are dependent on properties of the physiological environment and properties of the drug itself. Key physiological parameters include the dimensions of the GI tract, the volume and composition of fluid, the fluid hydrodynamics (i.e., flow rate, gastric-emptying rate, shear rate), and the properties of the intestinal membrane. Important drug properties include dose, solubility, pK_a, diffusion coefficient, permeability, and particle size. A more complete list of drug properties and physiologic properties that influence oral drug dissolution and absorption is provided in Table 1.

Composition of the Gastrointestinal Fluid

Gastrointestinal fluid is a complex, dynamic mixture of components from a number of different sources within the gastrointestinal tract. Gastric fluid is made up of saliva, gastric secretions, dietary food and liquid, and refluxed liquid from the duodenum. The gastric fluid composition changes as the fluid is mixed and delivered to the duodenum. Some major components of gastric fluid important for drug disposition include hydrogen ion concentration, bile salts, lipase, and the protein-digesting enzyme pepsin (Refer to Tables 2 & 3 for a summary of components and concentrations.). The concentration of hydrogen ions affects the pH and thus the dissolution of some ionizable drugs. Pepsin may interfere with the stability of proteins and peptides, while lipase may affect drug release from lipid-based dosage forms[2]. Bile salts can combine with lipids to form mixed micelles, enhancing the solubility of some drugs and may also decrease surface tension and thus enhance wetting[13].

Kalantzi et al. found median pepsin levels in the fasted state to range from 0.11–0.22mg/mL[14], while other researchers have found them to be between 0.1 and 1.3 mg/mL[15–16]. Pepsin in the fed state is typically higher and has been shown to range from 0.26 to 1.72 mg/mL[14, 16]. The concentration of hydrogen ions, which are secreted by the stomach in the form of hydrochloric acid is reflected in the pH, which is typically 1–2 in the fasted state (0.01–0.1 M) and ranges from about 3–7 in the fed state (10^{-3} – 10^{-7} M). Vertzoni and co-workers state that gastric lipase is probably not important in the fasted state since it is active

in the pH range of 3–6 and is thought to be present at concentrations of 0.1mg/mL[17]. Lipase activity in the fed stomach has been shown to range from 11.4–43.9 U/mL[18]. Bile salt levels have been found to be about 0.08 to 0.275 mM in the fasted stomach[17, 19] and 0.06 mM in the fed stomach[20]. Vertzoni and co-workers recently measured the relative amounts of individual bile salts in the fasted stomach and found glycochenodeoxycholate and glycocholate to predominate[19]. Bicarbonate concentrations in the fasted stomach have been shown to range from 7 to 20 mEq/L[21–22].

The composition of the fluid in the upper small intestine is made up of chyme from the stomach, as well as secretions from the liver, the pancreas, and the wall of the small intestine. Composition is affected by fluid compartmentalization, mixing patterns, absorption of fluid into the intestinal wall, and transit down the intestinal tract. Secretions from the pancreas include bicarbonate as well as proteases (the major ones are trypsin and chymotrypsin), amylases, and lipases[23]. The liver secretes bile, which contains bile salts, phospholipids, bicarbonate, cholesterol, bile pigments, and organic wastes. The wall of the small intestine secretes mineral ions such as bicarbonate, sodium, and chloride, as well as water. Bicarbonate is secreted to neutralize gastric secretion in the GI lumen and by the duodenal epithelial cells to protect the duodenal epithelium from acid-related damage[24]. The buffer species in the gastrointestinal media can significantly affect the dissolution rates of ionizable drugs[25].

As food intake triggers many of the secretions in the small intestine, the composition of fed state intestinal fluid can vary greatly from fasted state intestinal fluid. This difference in composition can be partially responsible for differences in bioavailability seen when drug is administered in the fed versus the fasted state. For some lipophilic drugs, coadministration with a meal has been shown to increase bioavailability compared to the fasted state. Sunesen et al. showed that the oral bioavailability of the poorly soluble drug danazol was three-fold higher when taken with a high-lipid meal compared with 200 mL of water[26]. However, in some cases the oral bioavailability can be negatively affected due to chelation of a drug with food components[27].

The increased bioavailability seen for some drugs in the fed state can be attributed to the enhanced solubilizing capacity of intestinal fluids due to bile and pancreatic secretions and the presence of exogenous lipid products[28]. For instance, dietary triglycerides are hydrolyzed into free fatty acids and monoglycerides in the duodenum mainly due to pancreatic lipase, and the free fatty acids combine with bile salts to form mixed micelles, which can be transported to the intestinal membrane[29]. Many instances of enhanced solubility and dissolution due to mixed micelles formed by bile secretions, and lipolysis products formed in the fed state exist in the literature[30–32].

Concentrations of lipolytic products, bile salts, and phospholipids in the upper small intestine tend to show high variability with time and between study subjects[14, 33]. Lipolytic product concentrations have ranged from 0–1.8 mg/mL in the fasted and 0.5–100 mg/mL in the fed upper small intestine[18, 33]. After administration of Ensure Plus® (fed), and Scandishake Mix® (fat-enriched fed) Clarysse et al. found the dominant lipolytic products in the duodenum to be monoglycerides, which accounted for 5–88% of total lipids, followed by free fatty acids[33]. Phospholipid concentrations have ranged from 0.03–0.6 mM in the fasted[33–34] and 0.8–3 mM in the fed state [33, 35]. Bile salt concentrations have ranged from 0.6–17 mM [2, 33] and 1.6–40 mM[36–37] in the fasted and fed states, respectively. Clarysse et al. found duodenal bile salts to be made up of cholate and chenodeoxycholate (which comprised about 65%) as well as deoxycholate and ursodeoxycholate[33], while Vertzoni found the major bile salts in the duodenum to be glycodeoxycholate, glycochenodeoxycholate, and glycocholate in the fed state[19]. Concentrations of lipolytic

products and phospholipids in the ileum are unavailable, but bile salt concentrations have ranged from 2–10 mM and 0.2–30 mM in the fasted and fed states, respectively[36, 38].

The concentration of bicarbonate in the small intestine is dynamic and depends on location and prandial state. The bicarbonate concentration in the fasted state has ranged from about 2 to 30 mM in the duodenum and jejunum and 30–75 mM in the ileum[39–43]. Values in the fed state are less abundant. Rune and co-workers reported a value of 10 mEq L^{-1} in the fed duodenum[44].

Properties of the Gastrointestinal Fluid

pH

The pH of the GI fluids in the local region of the intestine will influence a drug's dissolution rate and possibly its permeability[4]. The pH strongly influences the solubility of weak electrolytes by determining their ionization state. When the pH is such that a drug is in its ionic form, the drug behaves like a strong electrolyte and solubility is usually high compared to its nonionized form[45]. The pH thus has a strong effect on the dissolution of drug products, especially those with pK_a values within the physiological range. This phenomenon has been demonstrated for different types of dosage forms such as immediate- and modified-release[46–48].

The pH in the gastrointestinal tract is a function of many variables including prandial condition, time, meal volume and content, and volume of secretions, and it varies along the length of the GI tract (Refer to Table 3 for a summary of pH values in the stomach, duodenum, jejunum and ileum.). The gastric pH in the fasted state has been recorded between 1 and 8 for individuals[49–50], with typical median values falling between about 1 and 2[14, 51]. Dressman et al. found gastric pH to remain below pH 2 68% of the time and below pH 3 90% of the time[51]. Shortly after ingestion of a meal, the pH has been shown to rise to about 6.0–7.0, and decreases back to fasting levels after approximately one to four hours, depending on factors such as meal composition, amount, and pH[14]. Gastric pH values in the fed state have ranged from 2.7–6.4[14, 51]. An approximation of a typical gastric pH profile as measured by Dressman et al. [51] is shown in Figure 1.

Average pH values in the fasted upper small intestine have been reported to range from about 4 to 8[52, 50], with typical values around 6.5[52–54]. Clarysse et al. found duodenal pH in the fasted state to display considerable intra- and inter-subject variability as shown in Figure 2[33]. In the ileum pH has be reported as 6.5–8 in the fasted state [55–56].

The pH in the upper small intestine tends to be lower in the fed compared to the fasted state. As is found in the fed stomach, the pH in the upper small intestine tends to rise after meal intake and slowly decreases over time. Average values have been shown to vary from about 3 to 7[14, 51], with typical median values around 5 during the later post-prandial stage[56–57]. Kalantzi et al. found the pH in the distal duodenum to decrease from 6.6 to 5.2 over the first 210 min following administration of Ensure Plus®[14]. Fed pH values in the ileum have been reported in the range of 6.8–8[58]. Clarysse et al. found the pH of the administered meal to have a strong impact on local pH, leading to decreased intersubject variability compared to the fasted state during the first 3 hours after meal intake[33]. They found the pH to decrease with time, with minimum individual values of 3.9–4.9, returning to fasting values after about 300 min after meal ingestion. Plots of individual and median pH versus time for the five healthy volunteers in the fasted and fed states as measured by Clarysse et al. are given in Figure 2.

Buffer capacity

The buffer capacity of the gastrointestinal fluid can affect the dissolution rate, particularly for ionizable drugs. The higher the buffer capacity, the more the buffer will influence pH changes at the drug-liquid interface (i.e., the surface pH)[25]. The buffer capacity depends on the pH of the fluid, the pK_a of the buffer, and the buffer concentration.

Kalantzi et al. found the median buffer capacity in the stomach to be 7 mmol L^{-1} ΔpH^{-1} 20 min after administration of water and 18 mmol L^{-1} ΔpH^{-1} at later time points (fasted-state conditions)[14]. In the fed state (after ingesting 500 mL Ensure plus), they found median values of gastric buffer capacity to increase from 14 to 28 mmolL^{-1} ΔpH^{-1} over a 30- to 210-min sampling period. They also found intersubject variability to increase with time after meal administration. Values for buffer capacity in the small intestine have ranged from 2–13 mmol/L/pH in the fasted state[35, 53], and 13–30 mmol/L/pH in the fed state[14, 35]. While buffer capacity in the fed ileum is not available, Fadda and co-workers reported buffer capacity in the fasted state to be 6.4 mmol/L/pH[59]. Buffer capacity values found in the literature are summarized in Table 3.

Osmolality

Osmolality can affect drug release and excipient performance[6]. Delayed dissolution of 5-aminosalicylic acid from Eudragit L coated tablets was shown at higher osmolality[60]. Gastric osmolality in the fasted state has been shown to range from 29–276 mOsm/kg[61–62]. Kalantzi et al. found gastric contents in the fasted state to be hypoosmotic, with lower values of 98 mOsm/kg at early time points, plateauing to 140 mOsm/kg at later times. After a meal, Kalantzi et al. found the median value in the stomach to be 559 mOsm/kg after 30 min and 217 mOsm/kg after 210 min, with variability decreasing with time after the meal[14].

In the upper small intestine, osmolality values range from 124–278 mOsm/kg in the fasted state[33, 63], and 250–367 in the fed state[33]. Clarysse et al. found variability in osmolality to be higher in the fed compared to the fasted state, with high fed state fluctuations until 240 min after food intake[33]. They found fasted state values to be hypoosmotic or close to isoosmotic, with an overall median value of 224 mOsm/kg. In the fed- and fat-enriched-fed states they found values to be hyperosmotic during the first three hours post-prandially, with isoosmotic overall median values of 285 and 278 mOsm/kg, respectively. Jantratid and co-workers also state that osmolality in the distal duodenum increases slightly during the first 120 min after meal intake, and then gradually equilibrates to isoosmotic[6]. Osmolality values in the stomach and upper small intestine are provided in Table 3. Literature values of osmolality in the ileum could not be found.

Surface tension

Surface tension can affect dissolution by influencing wetting of the dosage form[13], with a higher surface tension leading to decreased wetting. Gastric surface tension values in the fasted and fed states range from about 41–46 and 30–31 mN/m, respectively[14]. In the upper small intestine, surface tension values range from 28–46 mN/m in the fasted state, and 27–37 mN/m in the fed state[33, 35]. Surface tension values in the ileum are not available.

Viscosity

Measurement of the viscosity of fluids can be complex. Simple fluids such as water, tea, coffee, simple syrups and edible oils behave as Newtonian fluids where viscosity is constant (i.e., shear rate is proportional to shear stress)[64]. However, many liquefied foods and biological fluids demonstrate non-Newtonian flow behavior meaning that viscosity is dependent upon shear rate, often exhibiting decreased viscosity with increased shear rate (i.e., shear thinning)[64] For non-Newtonian fluids it is therefore important to know the shear

rate at which the viscosity is measured. In part for these reasons, measured values of GI fluid viscosity for humans in the fed and fasted states are very limited. The viscosity of water at 37°C is 0.691 cP (1cP = 1 mPa-s), while the viscosity of various test meals consisting of dietary fibers (e.g., methylcellulose, bran, psyllium, and guar gum) are often administered in solutions with viscosities that range from 10 to >10,000 cP[64–66]. Typical meals have therefore been characterized to have viscosities in the range of 10 to 2000 cP[65, 67]. Marciani and coworkers utilized echo-planar Magnetic Resonance Imaging (MRI) in humans to monitor changes in viscosity of viscous meals and demonstrated significant and rapid reductions in viscosity with time due to dilution by gastric fluids[64]. Viscosity is also influenced by pH in addition to soluble meal content and concentration. Increased viscosity has been shown to generally decrease stomach emptying and prolong GI transit and has been shown to influence blood glucose and cholesterol levels[65, 68].

Temperature

The temperature of GI fluids also affects dissolution and absorption. It can affect the diffusion coefficients of the drug and buffer species, the drug solubility, and the bulk drug concentration. The average GI temperature is generally considered to be 37°C. Several researchers have found 37°C to be an accurate resting temperature, but temperature can increase slightly after exercise. Chin Leong Lim and co-workers used an ingestible telemetric temperature sensor to measure GI temperature during rest and exercise and found the average GI temperature of nine healthy male runners to increase from 37.6°C at rest to 39.3°C after running outside for 45 minutes[69].

Volume

The volume of liquid in the gastrointestinal tract affects the amount and potentially the concentration of dissolved drug. If the volume of liquid is such that the potential bulk concentration of drug exceeds the solubility of the drug, then only a small fraction of the original dose may go into solution. Like other GI parameters, the volume of liquid in the various compartments can vary within and between individuals as well as with time and prandial state. It is affected by the amount of liquid ingested, the volume of gastric and pancreatic secretions, gastric-emptying rate, intestinal transit time, as well as uptake and efflux of liquids along the GI membrane.

Volume of liquid in the stomach depends on the amount of liquid ingested, the rate and amount of secretions, and the rate at which it empties into the small intestine. Using MRI, Steingoetter and co-workers measured liquid volumes in the fasted stomach before and after ingesting 300 mL of water and found them to be 28 (18–54) mL before water and 296 (279–323) mL after water[70]. However, in another study when Kwiatek et al. examined the ratio of the initial postprandial liquid volume in the stomach to the volume of the infused meal (nutrient drink), they found it to decrease as a function of infused meal volume (ratios of 1.25, 0.95, 0.92, and 0.83 for 200-, 400-, 600-, and 800-mL meal volumes, respectively)[71]. They attributed this progressive decrease in initial gastric volume as a function of meal volume to a larger proportion of liquid nutrient passing into the small intestine during a rapid, early emptying phase. After their measurements of initial volume, they also found the gastric volumes to increase further (due to gastric secretions) before volumes started to decline. They found this increase to be independent of caloric load and greater for the smaller rather than the larger infused meal volumes, demonstrating a slower rate of emptying compared to rate of secretion for the smaller volumes, but a faster rate of emptying compared to rate of secretion for larger volumes. For study participants in a seated position, Steingoetter and co-workers found the contents to be distributed throughout the proximal and distal portions of the stomach, with a distal-to-proximal ratio of 0.23 upon ingestion of the water and 0.58 after 30 min.

Liquid volume in the small intestine depends on the amount of liquid emptying from the stomach, absorption of fluid through the intestinal wall, and intestinal transit time. Volume in the fasted small intestine has been shown to range from 30–420 mL[72], with average values tending to fall near 100 mL in several studies[73–75]. It seems that fasting volumes in the small intestine are less dependent on the amount of liquid ingested than fasting volumes in the stomach. Volume in the fed small intestine has been recorded in the range of about 18 to 660 mL[73–74], and is more highly dependent on the amount and contents of the meal. Sutton recently modeled the mean plasma concentration profiles of four solubility-limited compounds using literature values of small and large intestinal liquid volumes[76]. On average a small intestinal liquid volume of about 130 mL (range of 10–150 mL) provided the best fits to the data, which is in agreement with the average small intestinal liquid volumes reported in the literature. Measured human gastric and intestinal liquid volumes from the literature are provided in Table 4.

Schiller et al. used MRI to show that the GI lumen does not represent a continuous watery compartment[72]. Instead, they found the free water content to exist as fluid pockets. In the fasted small intestine they found the mean number of fluid pockets to be equal to 4, with a median volume of 12 mL per fluid pocket (Refer to Table 5.). In the fed small intestine the mean number of fluid pockets was 6, with a 4-mL median volume per pocket. In addition, they found the volume of free liquid to be lower in the fed than in the fasted state. Schiller et al. also showed that non-disintegrating capsules ingested prior to MRI acquisition were not completely surrounded by fluid in both the stomach and small intestine in the fasted and fed states. In the fasted small intestine only fifty-percent of ingested capsules (14 out of 28 capsules across multiple subjects) were completely surrounded by fluid. In the fed small intestine 1 out of 5 capsules were completely surrounded by fluid.

Based on these results, it is possible that the volume of water a dosage form is in contact with is less than the volumes shown in Table 4. In addition, a dosage form may not be exposed to fluid during the entire time it spends in the GI tract. Both scenarios could decrease the solubility and dissolution rate and could lead to an inhomogeneous concentration of drug in the GI lumen. Consequently, the absorption rate of the drug into the GI membrane may not be adequately predicted, as the drug concentration at the intestinal wall may not be similar to the bulk drug concentration.

Hydrodynamics

GI hydrodynamics are partially dependent on contractions in the stomach and small intestine, as well as the amount of liquid and solids present. Layers of smooth muscle contract in a coordinated, rhythmic motion. The contractions cause motility that propels food through the GI tract in a peristaltic motion, mixes chyme within the GI lumen, and juxtaposes chyme with the brush border of the enterocytes. Smooth muscle also causes intestinal villi to undulate, agitating the unstirred layer of fluid associated with the brush border of the enterocytes[11]. Contractile activity typically initiates in the antrum and migrates distally through the duodenum of the small intestine. The autonomic nervous system and various digestive system hormones control the contractions.

Contractility in the fasted state is characterized by cyclical fluctuations. The cycle comprises three well-defined phases, including a quiescent phase (phase I), a phase of intermittent and irregular contractions that gradually increase in strength (phase II), and a short period of intense contractions (phase III)[77]. This cyclical contractility pattern is called the Migrating Motility Complex (MMC). The MMC can initiate not only in the stomach, but also at various points along the esophagus and small intestine, with the incidences varying in the

different segments[10]. The total cycle typically lasts approximately 90–120 min, but has been shown to range from 15–180 min[78].

In the fed state, the MMC is replaced by regular, tonic contractions that propel food toward the antrum and mix it with gastric secretions[79]. During these contractions fine particles and liquids pass from the stomach to the duodenum, while larger particles are retro-pulsed back into the body of the stomach. Once the meal has been emptied from the stomach, the MMC resumes. Gastrointestinal motility influences the gastric emptying rate, intestinal transit time, and mixing patterns of solids and liquids in the stomach and intestine[80–83].

Gastric-emptying rate and forces

The gastric emptying rate defines the rate at which liquids and solids empty from the stomach into the upper small intestine. It determines the residence time of a drug in the stomach as well as the rate at which the drug is introduced into the small intestine. As most drugs are absorbed primarily in the small intestine, the rate and extent to which dissolved drug is presented to this segment influences drug absorption, and thus onset of the desired therapeutic response. Gastric emptying can be the rate-limiting step in absorption for rapidly dissolving, immediate-release BCS I drugs[84].

In the fasted state, the MMC greatly regulates gastric emptying rate, while in the fed state gastric emptying is influenced by low-amplitude contractions as well as pyloric resistance and duodenal feedback mechanisms[77]. In both the fasted and fed states, emptying rate also depends on the amount of liquid or solid ingested, the size/nature of the liquid or solid ingested, and the phase of contraction during which the liquid or solid was ingested (Refer to Table 6 for a summary of gastric residence times from the literature).

Non-nutrient liquids do not normally interrupt the MMC and are typically emptied in an exponential pattern[70, 79]. Granger and co-workers showed that the half-time for saline emptying from the human stomach is 12 min[85], and Steingoetter and co-workers found the half-time for emptying 300 mL of water to be 15.8 min[70].

Gastric emptying postprandially is largely dependent on meal size and composition[79]. When nutrient liquids or solid meals are ingested, the MMC can be interrupted due to feedback mechanisms in the duodenum. A 25% glucose solution has been shown to empty in 75 min in humans[79]. Kwiatek and co-workers found gastric emptying half time to decrease with increasing nutrient liquid volume and increase with increasing calorie load[71] as shown in Table 7. Dressman et al. summarized typical solid-meal half-emptying rates in humans from the literature and found them to range from 70–130 min[79].

It is thought by many researchers that beyond a size of 2–7 mm, gastric emptying of solid dosage forms or solid particulates differs from that of liquids and occurs mainly during phase II and III of the MMC[84]. Bass showed that single tablets ranging in diameter from about 5–13 mm typically left the stomach between 5 and 120 min (the average MMC cycle time), although times ranged from 5 to over 200 min, with high intrasubject and intersubject variability[77]. Rhie et al. demonstrated that gastric emptying of 0.7 mm caffeine pellets happened during the fed state, while 3.6 mm acetaminophen pellets emptied following the onset of phase II contractions in the fasted state[86]. Using modeling, Higaki et al. found gastric emptying of 0.7 mm caffeine pellets in the fed state to be regulated by gastric motor activity, with absorption kinetics closely related to the gastric-emptying profiles. Podczeck et al. showed that 3-mm- and 10-mm-diameter tablets emptied after food (dextrose solution, beef solution, or shepherd's pie) had left the stomach, and that the influence of tablet diameter on median emptying time was significantly less than the influence of administering solid food (shepherd's pie) compared to liquid meals (dextrose or beef solutions)[87].

The forces to which tablets are exposed in the stomach were evaluated in both the fed and fasted states by Kamba and coworkers[88]. They utilized specially designed Teflon tablets with predetermined crushing strengths to evaluate these forces. They found that tablets with a crushing strength of 1.5 N were crushed in all four subjects under fed conditions and two of five subjects under fasting conditions. Tablets with a higher crushing strength of 1.89 N were crushed in two of six subjects under fed conditions and zero of five subjects under fasting conditions. The authors reasoned that the lower crushing forces in the fasted state occurred because of the open pylorus, resulting in lower overall forces being applied to the stomach contents. Laulicht and coworkers also investigated gastric forces using a magnetic tracking system[89]. The average human gastric emptying force was 414±194 dyn in the fasted state, which was statistically insignificantly lower than the 657±84 dyn measured in the fed state. Corresponding area normalized gastric emptying pressures were approximately 600 dyn/cm^2 in the fasted state and 960 dyn/cm^2 in the fed state.

Intestinal transit time and flow rate

The transit time (i.e., residence time) of a drug in the intestinal tract is a strong determinant of dissolution and absorption. It affects the amount of time a drug has to dissolve and absorb in the GI tract. The transit time of a dosage form in different segments of the GI tract is dependent upon factors such as gastric emptying rate and flow rate, and can vary significantly for even a single individual. Weitschies et al. performed a study on one individual in which they administered a non-disintegrating capsule to a volunteer on several separate occasions and monitored it using magnetic marker monitoring[90]. As shown in Figure 3, the variability in residence times in different segments of the GI tract was high even for a single individual. Refer to Table 6 for a summary of intestinal residence times from the literature.

Transit time in the small intestine is often quoted to be 3–4 h. McConnell and co-workers found times to range from 0.5–5.4 h with a mean of 3.2 h for a single individual given a 1–1.4-mm ethylcellulose –coated pellet on eight separate occasions[10]. Based on a review of the literature they stated that food has generally not been associated with changes in transit time in the small intestine.

Davis et al. completed a meta-analysis of transit data and found no difference in the intestinal transit times of tablets, pellets, and liquids[91]. Coupe et al. found transit times in the small intestine to range from 2.2 to 5.9 h for pellets and 0.9–6.2 h for 11.5-mm tablets[92].

The mean intestinal flow rate during fasting for all three phases of the MMC was shown to be 0.73 mL/min in the jejunum and 0.33 mL/min in the ileum (the flow rate in the duodenum was too fast to measure)[93]. The flow rates were shown to increase postprandially, with a value of 3.0 mL/min in the jejunum and 2.35 mL/min in the ileum[93]. Granger and co-workers stated that chyme traverses the small intestine in humans at a rate of 1–4 cm/min, with the velocity being faster in the duodenum and proximal jejunum compared to the ileum[85]. Table 6 includes a summary of intestinal transit times and flowrates from the literature.

Intestinal transit time is especially important for dosage forms that are not fully absorbed, as a change in contact time with the absorption area will result in a change in the fraction absorbed. While in general an increase in transit time will lead to an increase in the absorption of poorly or incompletely absorbed drugs, absorption can be decreased in cases where transit time is slowed because of an inhibition of smooth muscle motility due to a decrease in agitation of the unstirred layer[11].

Geometry & Composition of Intestinal Membrane

Surface area

Absorption rate is a function of the gastrointestinal surface area over which the drug is exposed. Generally speaking, a larger surface area would lead to a greater absorption rate. Drugs are rarely absorbed in the stomach due to its small surface area and short residence times[94]. The small intestine is the major site of drug absorption due to its large surface area and longer residence times. The mucosal surface of the small intestinal lumen is convoluted. Finger-like projections called villi extend from the luminal surface, and each villus is covered with smaller microvilli. Together, the convoluted mucosa along with the villi and microvilli increase the surface area of the small intestine approximately 600-fold above that of a flat tube of the same overall length and diameter[23]. These anatomical modifications increase the surface area of the duodenum and upper jejunum to a greater extent than the ileum, with the majority of surface area in the small intestine found in the jejunum[11].

While the absolute surface area in the small intestine is quite large as described above, the geometric surface area (calculated solely based on the overall length and diameter of the intestine) may be a better estimate of the area of exposure for a dosage form, as it more accurately reflects the surface area of the unstirred layer which is a barrier to drug absorption. Absolute and geometric surface areas, as well as geometries are included in Table 4.

Nature of intestinal membrane and absorption mechanisms

Absorption of drugs in the GI tract occurs mainly in the intestine. Several positive factors help drive absorption, including a concentration gradient, electrochemical potential difference, and hydrostatic pressure gradient between the intestinal lumen and the membrane[95]. In addition, several other factors deter drug absorption, including the physical barrier of the intestinal mucosa as a result of tight junctions and the lipid composition of the membrane, as well as biochemical barriers such as the presence of metabolizing enzymes and efflux transporters[95].

The pathways for drug absorption include carrier-mediated transcellular transport, vesicular transport, passive paracellular transport, and passive transcellular transport. In carrier-mediated transcellular transport, influx transporters expressed on the mucosa actively carry drugs across the membrane. The vesicular transport route includes fluid-phase endocytosis, receptor-mediated endocytosis, and transcytosis. In the passive paracellular route, drug absorption occurs through an extracellular route across the epithelium. Diffusion is regulated by electrochemical potential gradients derived from concentration differences and by electrical and hydrostatic pressure gradients between the two sides of the epithelium[95]. Tight junctions are the main barriers to this type of absorption. Finally, passive transcellular transport occurs when drugs move across the apical membrane, through the cytoplasm, and across the basolateral membrane. The surface area available for this type of transport makes up 99.9% versus 0.01% for the passive paracellular pathway[95].

As mentioned above, enzymes expressed on enterocytes can metabolize some drugs, causing a decrease in absorption. In addition, drugs can be metabolized or degraded in the GI lumen. In addition, efflux transporters mediate the transfer of some compounds from the cytoplasm back into the intestinal lumen. These factors all decrease the net absorption of drugs in the intestinal membrane and thus lower the potential bioavailability.

Physiological dissolution methodologies

Simulated gastric and intestinal fluids are media designed to mimic the major characteristics of *in vivo* fluids. Simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) were described in the USP as early as 1955[96]. As our knowledge of GI physiology has increased over the years, these fluids have been updated to more closely mimic *in vivo* characteristics. The most recent update by Jantratid and co-workers presents the most up-to-date fluids (Refer to Tables 8 and 9.) and summarizes some of the changes made over the years[6]. Jantratid and co-workers have proposed the use of "snapshot media" to simulate both gastric and intestinal fluids during different stages after meal consumption. Despite some potential drawbacks, simulated gastric and intestinal fluids make dissolution testing more physiological compared to using simple buffers and a number of successful IVIVCs have been generated using these fluids[97–98].

While existing *in vitro* systems partially address some of the major fluid components by utilizing simulated fluids, existing dissolution and dosage form testing methodologies generally fail to adequately address physiologically relevant hydrodynamics of fluid flow, shear and viscosity[2, 6, 67]. New, innovative dissolution methodologies that are more reflective of *in vivo* hydrodynamics and fluid content in the human intestinal tract are needed. Current dissolution methodologies produce variable and generally extremely high fluid velocities and thus "unrealistic" fluid flow (e.g., $5000<Re<10000$)[99–102], while current information on fluid flow in the human stomach and intestine indicate Re in the range of 1 to 30[67, 82–83, 103–104]. Novel dissolution methodologies that characterize dissolution under low Re and fluid shear are required to better simulate dissolution *in vivo*.

Conclusions

Pharmaceutical solid oral dosage forms must undergo dissolution in the intestinal fluids of the gastrointestinal tract before they can be absorbed and reach the systemic circulation. Therefore, dissolution is a critical part of the drug-delivery process. The characteristics of the physiological environment such as buffer species, pH, bile salts, gastric emptying rate, intestinal motility, and hydrodynamics will significantly impact dissolution and absorption. While significant progress has been made since 1970, when the first compendial dissolution test was introduced, current dissolution testing does not take full advantage of the extensive physiologic information that is available. For quality control purposes, where the question is one of lot-to-lot consistency in performance, utilizing nonphysiological test conditions that match drug and dosage form properties with practical dissolution media and apparatus may be appropriate. However, where IVIVCs are desired, it is logical to consider and utilize knowledge of the *in vivo* situation. Physiologically relevant information must serve as a basis for the design of dissolution test methods and systems that are more representative of the human condition. As *in vitro* methods advance in their physiological relevance, better IVIVCs will be possible. *In vitro* systems can then be more effectively utilized to design dosage forms that have improved and consistent oral bioperformance.

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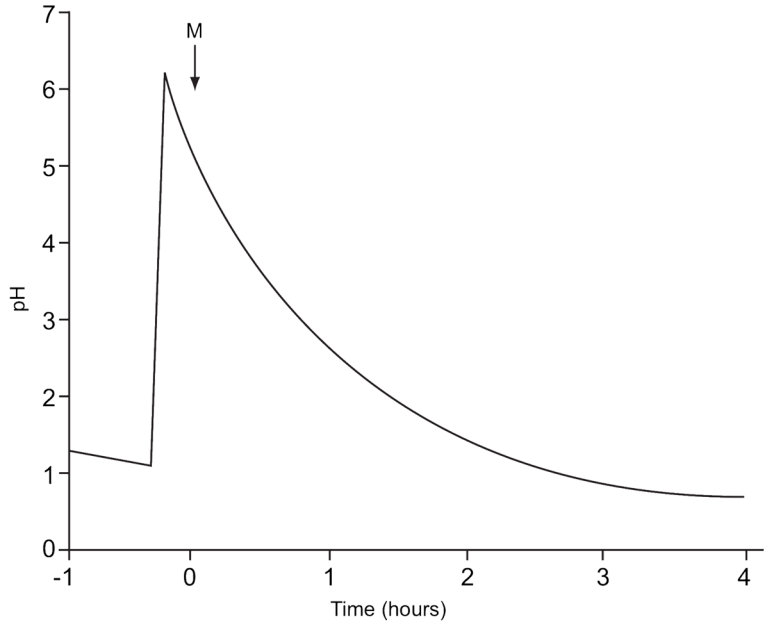

Figure 1.
Approximation of a typical pH profile in the stomach. The letter “M” denotes food intake (Redrawn from reference [51]).

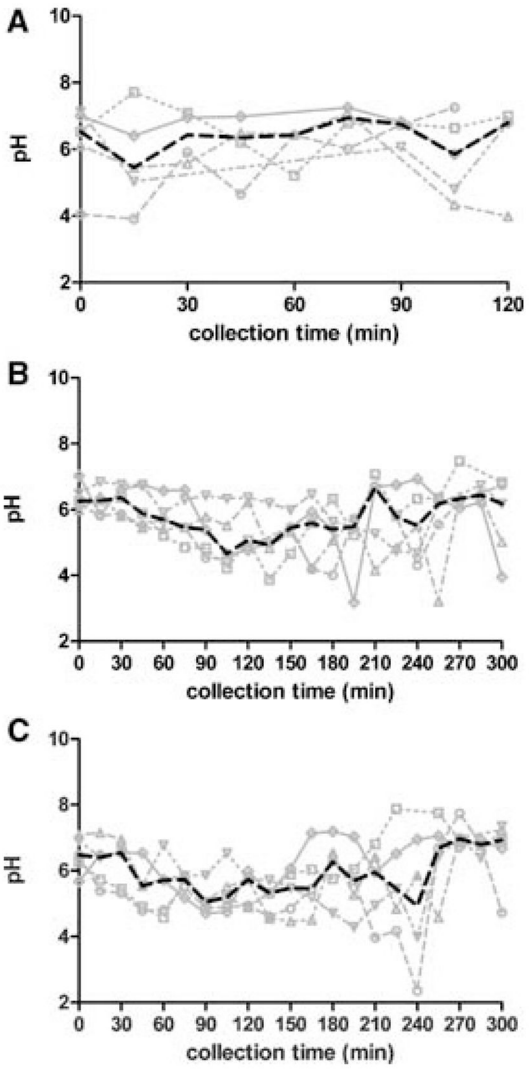

Figure 2.
Individual and median pH versus time in fasted (A), fed (B), and fat-enriched fed (C) state human duodenal fluid for five healthy subjects. Darkened lines represent median values[33]. (Reprinted from reference [33] with permission.)

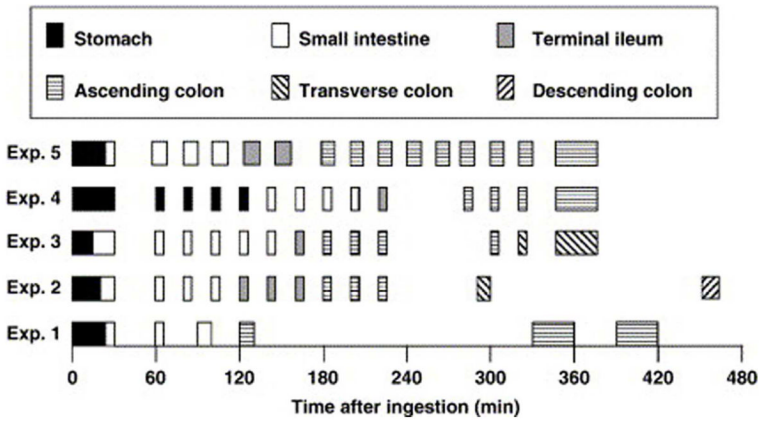

Figure 3.
Gastrointestinal transit of magnetically marked non-disintegrating capsules in a single volunteer after ingestion with 150 mL of water. Capsule taken after 8 h of fasting. Lunch served 240 min after ingestion of the capsule in experiments 1–4[90] (Reprinted from reference [90], with permission.).

Table 1

Drug properties and physiological properties that influence oral drug dissolution and absorption

Parameter	Drug properties	Physiological parameters
Drug diffusion coefficient, D	Radius, mass, volume	Solute concentration, temperature, fluid viscosity
Drug surface area, A	Particle size, size distribution, shape, state of particle aggregation	Fluid hydrodynamics
Length of hydrodynamic boundary layer (stagnant diffusion layer), h	Particle size, diffusion coefficient	Fluid velocity, viscosity, diffusion coefficients of diffusing species
Saturated solubility, C_s	Intrinsic solubility (molecular size, crystal properties, chemical groups), pK_a	Buffer species, buffer concentration, buffer capacity, pH, presence of lipolytic products, bile salts, and phospholipids, temperature
Bulk concentration, C_b	Dose, intrinsic solubility (molecular size, crystal properties, chemical groups), pK_a, intestinal permeability	Fluid volume (fluid ingested, gastric-emptying rate, transit time), absorption in GI membrane, buffer species, buffer concentration, buffer capacity, pH, presence of lipolytic products, bile salts, and phospholipids, temperature
Intestinal wall permeability, P_w	Absorption mechanism (Simple diffusion: lipophilicity, charge, polarity. Facilitated diffusion or active transport: affinity for membrane channels or pumps)	Intestinal segment, Composition of intestinal wall, number of channels or transporters, apparent permeability to mass transport (turbulence due to intestinal wall contractions)
Concentration at the intestinal wall, C_w	Dose, intrinsic solubility (molecular size, crystal properties, chemical groups), pK_a, permeability, diffusion coefficient	Hydrodynamics, viscosity, shear, transit time

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Table 2

Literature values for concentrations of some major components of fluid in the fasted and fed stomach and small intestine. The designation (e) indicates a value that was measured early in the post-prandial phase (between 0 and 60 minutes), (m) denotes a value measured in the mid post-prandial phase, and (l) denotes a value that was measured late in the post-prandial phase (greater than 100 minutes). Unless indicated next to the value, units are noted next to the name of the component.

			Stomach	Duodenum	Jejunum	Ileum
Bicarbonate (mEq L^{-1})	Fasted	Mean	7.3[a]	2.7[105], 6.7[106], 15[b]	17[105], 30[b], 30[c], 8.2±5 mM[d]	40[d], 50[107], 70[b], 74[108], 75[c], 30±11mM[d]
		Range	9–20[g]		2–20[e], 5–10[109], 6–20[f]	
	Fed	Mean		10[h]		
Bile salts (mM)	Fasted	Median	0.100[j]	2.7[k], 2.6[l]		
		Mean	0.08±0.03[l], 0.275[110], 0.081[m]	6.4±1.3[n], 4.3±1.2[n], 5.90±1.8[o]	2±0.2[p]	
		Range		1–5.3[q], 0.6–5.1[r], 0.3–9.6[j]	0.8–5.5[r], 0.1–13.3[j], 5–6[n], 0–17[n]	2–10[s]
	Fed	Median		3.6[j], 5.2[j], 8.3 (e)[j], 11.9 (e)[j], 11.2(e)[k], 5.2(l)[k]		1.0[t], 0.5[t]
		Mean	0.06[20]	14.5(e)[u], 5.2(m)[u], 16.2±1.5[111], 9.7±1[111], 9.1[m]	8[112], 15[112], 8±0.1[p], 6.5±0.9[111]	
		Range		1.6–6.2[j], 3.2–6.8[j], 6.7–13.4[o]	0.5–40[t](graph), 3–34[112]	0.5–30[t], 0.2–1.3[t]
Lipids (mg/mL)	Fasted	Median		0.5[j]		
		Mean	0.56[o]	0.6[o]	0.1±0.01mM[p]	
		Range		0–1.8[j]		
	Fed	Median		1.8[j], 2.6[j]		
		Mean			22±1mM[p]	
		Range	50 (l)[o], 150(e)[o]	0.5–4.6[j], 1.1–3.6[j], 55–100[o]		
Phospholipids (mM)	Fasted	Median		0.6[j]		
		Mean			0.2±0.07[p]	
		Range		0.1–1.5[j], 0.03–0.06[q]		

			Stomach	Duodenum	Jejunum	Ileum
	Fed	Median		1.8[j], 1.2[j]		
		Mean			3±0.3[p]	
		Range		1.3–2.4[j], 0.8–1.6[j]		
Pepsin (mg/mL)	Fasted	Median	0.11 (e)[k], 0.22 (m)[k]			
		Mean	0.87[v]			
		Range	0.83–1.27[w]			
	Fed	Median				
		Mean	1.25[v], 1.68[v]			
		Range	0.26–0.58[w], 0.56–1.72[w]			
Lipase	Fasted	Mean	~0.1mg/mL[x]			
		Range				
	Fed	Range	11.4–43.9 U/mL[o]			
Potassium (mM)	Fasted	Mean	13.4±3.0[i]		5.4±2.1[i], 4.8±0.5[43]	4.9±1.5[43]
Sodium (mM)	Fasted	Mean	68±29[i]		142±13[i], 142±7[43]	140±6[43]
	Fed	Mean			106±15[t], 101±17[t]	139±11[t], 133±8[t]
Chloride (mM)	Fasted	Mean	102±28[i]		126±19[i], 135±8[43]	125±12[43]
Calcium (mM)	Fasted	Mean	0.6±0.2[i]		0.5±0.3[i]	

[a] From reference [21].

[b] From reference [40].

[c] From reference [42].

[d] From reference [43].

[e] From reference [39].

[f] From reference [41].

[g] From reference [22].

[h] From reference [44].

[i] From reference [50].

[j] From reference [33].

[k] From reference [14].

[l] From reference [20].

[m] From reference [19].

[n] From reference [2].

[o] From reference [18].

[p] From reference [35].

[q] From reference [34].

[r] From reference [53].

[s] From reference [38].

[t] From reference [36].

[u] From reference [37].

[v] From reference [15].

[w] From reference [16].

[x] From reference [17].

Table 3

Literature values for properties of fluids in the fasted and fed stomach and small intestine. The designation (e) indicates a value that was measured early in the post-prandial phase (between 0 and 60 minutes), (m) denotes a value measured in the mid post-prandial phase, and (l) denotes a value that was measured late in the post-prandial phase (greater than 100 minutes). Unless indicated nest to the value, units are noted next to the name of the component.

			Stomach	Duodenum	Jejunum	Ileum
Buffer capacity (mmol L^{-1} pH^{-1}	Fasted	Median	7 (e)[a], 18[a]	5.6[a]		
		Mean			3.23[59]	6.4[b]
		Range		4–13[c]	2.4–2.8[d]	
	Fed	Range	14–28[a]	18–30[a]	13.2–14.6[d]	
Osmolality (mOsm kg^{-1})	Fasted	Median	98 (e)[a], 140 (l)[a]	178[a], 224[e]		
		Mean	29[f], 191±36[g], 33.6±5.9[h] 221±15[h]	142[f], 137±54[c]	271±15[g], 200±68[c], 278±16[h]	
		Range	171–276[i]	124–266[e]		
	Fed	Median	559 (e)[a], 217 (l)[a]	287[e], 276[e], >287 (e)[a], 287 (l)[a]		
		Range		250–367[e], 268–304[e]		
Surface tension (mN m^{-1})	Fasted	Median		32.3[a], 41.2[e]		
		Mean			28±1[d], 33.7±2.8[h]	
		Range	41.9–45.7[a]	33.3–46.0[e]		
	Fed	Median		34.2[e], 35.4[e]		
		Mean			27±1[d]	
		Range	30–31[a]	32.2–36.7[e], 33.7–36.0[e]		
Viscosity (cP)	Fasted	Range				
	Fed	Range	10–2000[j]			
pH	Fasted	Median	1.7[k], 2.4 (e)[a], 1.7 (l)[a], 1.8[143]	6.1, 6.2[a], 6.6[e], 5.63[113]	7.2[k]	
		Mean	2.9 ± 1.97[g]	6.71±0.44[l], 7.0±0.4[c], 4.9[m], 6.4±0.6[n]	6.8±0.4[c], 7.5[d], 7.1± 0.60[g]	6.5±0.2[o]

			Stomach	Duodenum	Jejunum	Ileum
		Range	1–2.5[p], 1.4–2.1[k], 1.23–7.36[a], 1.4–7.5[g]	5.8–6.5[k], 4.00–5.39[m], 5.17–6.10[n]	4.4–6.5[114], 5.3–8.1[k], 5.3–8.1[g]	6.8–8.0[q]
	Fed	Median	5.0[k], 6.4 (e)[a], 2.7 (l)[a]	5.4[k], 6.6 (e)[a], 5.2 (l)[a], 5.9[e], 6.1[e], 5.35[r]		
		Mean		5.2 (e)[m], 4.2 (l)[m]	6.2±0.2 (e)[115], 5.4 ± 0.2 (l)[115], 6.1[d]	7.5[116]
		Range	4.3–5.4[k]	3.1–6.7[k], 4.5–5.5 (e)[m], 3.9–4.8 (l)[m], 5.1–5.7 (e) [117], 5.3–6.1 (l)[117], 4.6–6.3[58]	5.2–6.0 (e)[m]	6.8–7.8[118], 6.8–8.0[s]

[a] From reference [14].

[b] From reference [59].

[c] From reference [53].

[d] From reference [35].

[e] From reference [33].

[f] From reference [61].

[g] From reference [50].

[h] From reference [63].

[i] From reference [62].

[j] From reference [67].

[k] From reference [51].

[l] From reference [52].

[m] From reference [57].

[n] From reference [54].

[o] From reference [55].

[p] From reference [49].

[q] From reference [56].

[r] From reference [58].

[s] From reference [58].

Table 4

Literature values for liquid volumes and geometry in the fasted and fed stomach and small intestine. Values for the small intestine are for the entire small intestine unless the value is contained in an individual column.

			Stomach	Small Intestine		
				Duodenum	**Jejunum**	**Ileum**
Volume (mL)	Fasted	Mean	28[a] 296 (300mL water)[a] 27[119]	86[b], 81[b], 112±27[c], 109 ± 36[c], 165±22[d], 105±72[e]		
		Range	18–54[a] 279–323(300mL water)[a] 21–33[119]	34–46[b] 37–130[b] 45–319[e]		
	Fed	Mean	250±23 (200mL) [f], 380±25 (400mL)[f], 555±30 (600mL)[f], 664±34(800mL)[f]	47[b] 381[b] 590±73[c] 54±41[e]		
		Range		18–78[b], 343–491[b], 20–156[e]		
Surface area (cm^2)	Absorbing[120]	Mean	525.58 ± 24.143[g], 1100[h]	10^4-1.2 X 10^4 (considering valves of keckring), 10^5 (considering villi), 2 X 10^6 (considering microvilli)		
				900[h]	600000[h]	600000[h]
	Geometric	Mean	942[i]	393[i], 197–490[j]	4712[i], 825–1319[j] 3300[120]	4712[i], 980–1862[j]
Length (cm)[120, k]	Anatomical	Mean			680	
		Range			255–1128	
		Mean			260	395
		Range		25–30		
	Physiological	Mean			282	
		Range			229–337	
		Mean		21	105	156
		Range		18–26		

			Stomach	Small Intestine		
				Duodenum	Jejunum	Ileum
Diameter (cm)	Absolute	Mean	15[h]	5[h], 4[120]	5[h]	5[h]
		Range		3.5–6[120]	2.5–4[120]	2–3.8[120]
	Cranial to caudal[120]	Mean	37			
		Range	29.5–49.5			
	Greatest diameter[120]	Mean	15			
		Range	6.5–21.5			
	Body[120]	Mean	11			
		Range	4–19			
	Pyloric antrum[120]	Range	4–5			

[a] From reference [70].

[b] From reference [73].

[c] From reference [74].

[d] From reference [75].

[e] From reference [72].

[f] From reference [71].

[g] Surface area of gastric mucosa.

[h] From reference [95].

[i] Calculated using length and diameter from reference [95] assuming cylindrical geometry.

[j] Calculated using absolute diameter and physiological length from reference [120] assuming cylindrical geometry.

[k] Anatomical lengths measured at autopsy or from material recovered from surgery and physiological lengths measured from living persons.

Table 5

Total volume, number and volume of liquid pockets, and proximity of capsules to liquid-filled regions in the fasted and fed small intestine (Reproduced from reference [72].). Fasting conditions and 1 hour after a meal (n=12)[72].

Condition		Fasted	Fed
Total volume of liquid (mL)	Mean±s.d	105±72[a]	54±41[a]
	Range	45–319	20–156
	Median	83	39
	Individual (approx.)[b]	45, 48, 69, 73, 77, 81, 85, 94, 113, 115, 130, 319	20, 22, 26, 28, 30, 38, 44, 50, 70, 75, 101, 156
Number of liquid pockets	Mean	4[c]	6[c]
	Individual (approx.)[b]	2, 3, 4, 5, 8	2, 5, 6, 7, 11
Volume of liquid pocket (mL)	Median	12[d]	4[d]
Number of capsules surrounded by liquid	No./Total	14/28	1/5
Number of capsules partially surrounded by liquid	No./Total	6/28	1/5
Number of capsules not in contact with liquid	No./Total	8/28	3/5

[a] P<0.01.

[b] Approximate values read from graph.

[c] P<0.05.

[d] P<0.001

Table 6

Literature values for residence time in the stomach, residence time in the small intestine and small intestinal flow rates.

Time for half-emptying - stomach (min)	Fasted	Mean	15.8 (300mL water)[a], 12 (saline)[b], 75 (glucose)[c]
		Range	11.5–17.0 (300mL water)[a]
	Fed	Mean	44±15 (liquids)[121], 105±21 (solids) [121], 40±13[121], 32±7 (liquids)[122], 46±9 (liquids)[122], 67±9 (liquids)[122], 76±6 (liquids)[122], 72[d], 69[d]
		Range	69–93[d], 50–76[d]
Time for complete emptying - stomach (min)	Fasted	Mean	25[a]
	Fed	Mean	40[d]
Transit time - entire small intestine (min)	Fasted	Mean	192 (coated pellets)[e]
		Range	90–324 (coated pellets)[e], 132–354 (pellets)[f], 54–372 (tablets)[f]
	Fed	Mean	276±99 h (liquids) [121], 342±120 h[g]
		Range	
Transit time - duodenum to jejunum (min)[123],	Fed	Mean	32±3 (40kcal/h) 30±1 (90kcal/h), 32±2 (160kcal/h)
Transit time - duodenum to ileum (min)[123]	Fed	Mean	59±2 (160kcal/h), 47±3 (40kcal/h), 47±2 (90kcal/h)
Flow rate - jejunum (mL/min)[h]	Fasted	Mean	0.73
	Fed	Mean	3.0
Flow rate – ileum (mL/min)[h]	Fasted	Mean	0.33
	Fed	Mean	2.35

[a] From reference [70].

[b] From reference [85].

[c] From reference [79].

[d] From reference [73].

[e] From reference [10].

[f] From reference [92].

[g] From reference [49].

[h] From reference [93].

Table 7

Effects of meal volume and caloric load on the half-emptying time of gastric contents (Reproduced from reference [71].). Data and standard error between any 2 volumes (in parenthesis) were estimated from mixed-effects model. The standard errors for differences between 2 volumes are given in parenthesis[71].

	Meal Volume (mL)			
Caloric load (kcal)	**200**	**400**	**600**	**800**
200	56 (7)	41 (8)	42 (8)	38 (8)[a]
300	74 (7)[+]	59 (8)[b]	60 (8)[b]	56 (8)[a,b]
400	92 (7)[+]	77 (8)[b]	78 (8)	74 (8)[a,b]

[a] $P \leq 0.05$ vs. 200 mL

[b] $P < 0.01$ vs. 200 kcal[71].

Table 8

Evolution of fasted and fed simulated gastric fluids.

Fluid name	**USP SGF, TS[96]**	**FaSSGF[a]**	**N/A[b]**	**FeSSGF[b]**	**N/A[b]**
Prandial state	Fasted	Fasted	Fed (early)	Fed (middle)	Fed (late)
Year	1955	2005	2008	2008	2008
Buffer type	-	-	-	Acetate	Phosphate
Buffer concentration (mM)	-	-	-	46.9	37.5
pH	~1.2	1.6	6.4	5.0	3
Buffer capacity (mmol/L/pH)	-	-	21.33	25	25
Osmolality (mOsm/kg)	Not available	120.7 ± 2.5	559	400	300
Surface tension (mN/m)	50.81[124]	42.6	49.7 ± 0.3	52.3 ± 0.3	58.1 ± 0.2
Composition	Hydrochloric acid, 70 mM Pepsin, 3.2 g/L Sodium chloride, 34.2 mM	Sodium taurocholate, 80 μM Lecithin, 20 μM Pepsin, 0.1 mg/mL Sodium Chloride, 34.2 mM Hydrochloric acid, q.s.	Sodium chloride, 148 mM Milk:buffer, 1:0 Hydrochloric acid/Sodium hydroxide, q.s.	Sodium chloride, 237.02 mM Acetic acid, 17.12 mM Sodium acetate, 29.75 mM Milk:buffer, 1:1 Hydrochloric acid/Sodium hydroxide, q.s.	Sodium chloride, 122.6 mM Ortho-phosphoric acid, 5.5 mM Sodium dihydrogen phosphate, 32 mM Milk:buffer, 1:3 Hydrochloric acid/Sodium hydroxide, q.s.

[a] From reference [17].

[b] From reference [6].

Table 9

Evolution of fasted and fed simulated intestinal fluids.

Fluid name	USP SIF, TS[a]	USP SIF, TS[b]	FaSSIF[125]	FaSSIFm[126]	FaSSIF-V2[c]	FeSSIF[125]	FeSSIFc[126]	FeSSIF-V2[c]
Prandial state	Not specified	Fasted	Fasted	Fasted	Fasted	Fed	Fed	Fed (combin ed early, middle, late)
Year	1960[d]	1996	1998	2004	2008	1998	2004	2008
Buffer type	Phosphate	Phosphate	Phosphate	Maleate	Maleate	Acetate	Citrate	Maleate
Buffer concentration (mM)	50.0[d]	50.0	28.7	25.0	19.1	144	84	55.0
pH	7.5	6.8	6.5	6.5	6.5	5.0	5.0	5.8
Buffer capacity (mmol/L/pH)	Not available	18.4 ± 0.2 (w/o pancreatin)	12	12	10	76	76	25
Osmolality (mOsm/kg)	Not available	113	270±10	270±10	180±10	635 ± 10	635 ± 10	390 ± 10
Surface tension (mN/m)	Not available	Not available	Not available	Not available	54.3	Not available	Not available	40.5 ± 2
Composition	Monobasic potassium phosphate,50.0 mM[d] Sodium hydroxide, ~15.4 mM[d] Pancreatin, 10.0g/L Hydrochloric acid/ Sodium hydroxide, q.s.	Monobasic potassium phosphate, 50.0 mM Sodium hydroxide, ~15.4 mM Pancreatin, 10.0g/L Hydrochloric acid/Sodium hydroxide, q.s.	Sodium taurocholate, 3 mM Egg phosphatidyl choline, 0.75 mM Sodium dihydrogen phosphate, 28.66 mM Sodium hydroxide, ~13.8 mM Sodium chloride, 106 mM	Sodium taurocholate, 3 mM Egg phosphatidyl choline, 0.75 mM Maleic anhydride, 25.01 mM Sodium hydroxide, ~45 mM Sodium chloride, 109 mM	Sodium taurocholate, 3 mM Lecithin, 0.2 mM Maleic acid, 19.12 Sodium Hydroxide, 34.8 mM Sodium Chloride, 68.62 mM	Sodium taurocholate, 15 mM Egg phosphatidylcholine, 3.75 mM Acetic acid, 144 mM Sodium hydroxide, ~101 mM Sodium chloride, 173 mM	Sodium taurocholate, 15 mM Egg phosphatidylcholine, 3.75 mM Citric acid, 84 mM Sodium hydroxide, ~200 mM Sodium chloride, 206mM	Sodium taurocholate, 10 mM Lecithin, 2 mM Glyceryl monooleate, 5 mM Maleic acid, 55.02 mM Sodium oleate, 0.8 mM Sodium Hydroxide, 81.65 mM Sodium Chloride, 125.5 mM

[a] From reference [127].

[b] From reference [128].

[c] From reference [6].

[d] USP SIF, TS was first introduced in 1955 with a buffer concentration of 6.4 mM and a sodium hydroxide concentration of about 38 mM [96].