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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; gastrointestinal; bioperformance; oral drug delivery; physicochemical properties

Introduction

Pharmaceutical solid oral dosage forms 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]

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

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(1) Abdou, H. M. Effect of the Physicochemical Properties of the Drug on Dissolution Rate. In *Dissolution, Bioavailability and Bioequivalence*, 1st ed.; Gennaro, A., Migdalof, B., Hassert, G. L., Medwick, T., Eds.; Mack Publishing: Easton, PA, 1989; pp 56−72.

(2) Dressman, J. B.; Amidon, G. L.; Reppas, C.; Shah, V. P. Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms. *Pharm. Res.* **1998**, *15*, 11–22.

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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, nonphysiologic 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. Jantratid 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 bloodstream. However, the drug must dissolve before absorption can occur and 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 eq 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 eq 2, where A is the area available for absorption (i.e., membrane surface in contact with the drug) and m is mass.

$$J_w = P_w C_w \tag{1}$$

$$\text{absorption rate} = \frac{dm}{dt} = \iint_A P_w C_w \, dA \tag{2}$$

Factors that affect dissolution can be understood by examining the simple Noyes−Whitney equation, which describes

(3) *USP, The United States Pharmacopeia USP 31, the National Formulary NF 26*. The United States Pharmacopeial Convention, Inc.: Rockville, 2008.

(4) Amidon, G. L.; Lennernas, H.; Shah, V. P.; Crison, J. R. A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability. *Pharm. Res.* **1995**, *12*, 413–420.

(5) FDA, Guidance for Industry. *Waiver of the in Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*; U.S. Department of Health and Human, Food and Drug Administration (FDA), Center for Drug Evaluation and Research: Washington, DC, 2000; pp 1−13.

(6) Jantratid, E.; Janssen, N.; Reppas, C.; Dressman, J. Dissolution Media Simulating Conditions in the Proximal Human Gastrointestinal Tract: An Update. *Pharm. Res.* **2008**, *25*, 1663–1676.

(7) Carino, S. R.; Sperry, D. C.; Hawley, M. Relative Bioavailability Estimation of Carbamazepine Crystal Forms Using an Artificial Stomach-Duodenum Model. *J. Pharm. Sci.* **2006**, *95*, 116–125.

(8) Grassi, M.; Grassi, G.; Lapasin, R.; Colombo, I. Drug Dissolution and Partitioning. In *Understanding Drug Release and Absorption Mechanisms, a Physical and Mathematical Approach*; CRC Press: Boca Raton, 2007; pp 249−327.

(9) Vangani, S.; Li, X.; Zhou, P.; Del-Barrio, M.-A.; Chiu, R.; Cauchon, N.; Gao, P.; Medina, C.; Jasti, B. Dissolution of Poorly Water-Soluble Drugs in Biphasic Media Using Usp 4 and Fiber Optic System. *Clin. Res. Regul. Affairs* **2009**, *26*, 8–19.

(10) McConnell, E. L.; Fadda, H. M.; Basit, A. W. Gut Instincts: Explorations in Intestinal Physiology and Drug Delivery. *Int. J. Pharm.* **2008**, *364*, 213–226.

(11) DeSesso, J. M.; Jacobson, C. F. Anatomical and Physiological Parameters Affecting Gastrointestinal Absorption in Humans and Rats. *Food Chem. Toxicol.* **2001**, *39*, 209–228.

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, secretions), 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

the mass of drug dissolving as a function of time. The equation, for dissolution from a planar surface, is given in eq 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]

$$\text{dissolution rate} = \frac{dM}{dt} = -\frac{DA}{h}(C_s - C_b) \qquad (3)$$

Each of the parameters in eq 2, describing absorption, and eq 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 and 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 stomach to range from 0.11 to 0.22 mg/mL,[14] while other researchers have found them to be between 0.1 and 1.3 mg/mL.[15,16] Pepsin in the fed stomach is typically higher and has been shown to range from 0.26 to 1.72 mg/mL.[14,16]

(12) Florence, A. T.; Attwood, D. Properties of the Solid State. In *Physicochemical Principles of Pharmacy*, 2nd ed.; Chapman and Hall: New York, 1988; pp 21−46.

(13) Dahan, A. S.; Amidon, G. L. Gastrointestinal Dissolution and Absorption of Class II Drugs. In *Drug Bioavailability, Estimation of Solubility, Permeability, Absorption, and Bioavailability*, 2nd ed.; van de Waterbeemd, H., Testa, B., Eds.; Wiley-VCH: Weinheim, 2009; pp 33−51.

(14) Kalantzi, L.; Goumas, K.; Kalioras, V.; Abrahamsson, B.; Reppas, C. Characterization of the Human Upper Gastrointestinal Contents under Conditions Simulating Bioavailability/Bioequivalence Studies. *Pharm. Res.* **2006**, *23*, 165–176.

(15) Schmidt, H. A.; Fritzlar, G.; Dolle, W.; Goebell, H. Comparative Studies on the Histamine and Insulin Stimulated Acid Pepsin Secretion in Patients Suffering from Ulcus Duodeni and Control Persons. *Dtsch. Med. Wochenschr.* **1970**, *95*, 2011–2006.

(16) Lambert, R.; Martin, F.; Vagne, M. Relationship between Hydrogen Ion and Pepsin Concentration in Human Gastric Secretion. *Digestion* **1968**, *1*, 65–77.

Table 2. Literature Values for Concentrations of Some Major Components of Fluid in the Fasted and Fed Stomach and Small Intestine[a]

		stomach	duodenum	jejunum	ileum
Bicarbonate (mequiv L^{-1})					
fasted	mean	7.3[b]	2.7,[10] 6.7,[106] 15[c]	17,[105] 30,[c] 30,[d] 8.2 ± 5 mM[e]	40,[g] 50,[107] 70,[c] 74,[108] 75,[d] 30 ± 11 mM[e]
	range	9−20[h]		2−20,[f] 5−10,[109] 6−20[g]	
fed	mean		10[i]		
Bile Salts (mM)					
fasted	median	0.100[j]	2.7,[k] 2.6[l]		
	mean	0.08 ± 0.03,[m] 0.275,[110] 0.081[n]	6.4 ± 1.3,[o] 4.3 ± 1.2,[o] 5.90 ± 1.8[p]	2 ± 0.2[q]	
	range		1−5.3,[r] 0.6−5.1,[s] 0.3−9.6[k]	0.8−5.5,[s] 0.1−13.3,[j] 5−6,[o] 0−17[o]	2−10[t]
fed	median		3.6,[k] 5.2,[k] 8.3 (e),[k] 11.9 (e),[k] 11.2 (e),[l] 5.2 (l)[l]		1.0,[u] 0.5[u]
	mean	0.06[20]	14.5 (e),[v] 5.2 (m),[v] 16.2 ± 1.5,[111] 9.7 ± 1,[111] 9.1[n]	8,[112] 15,[112] 8 ± 0.1,[q] 6.5 ± 0.9[111]	
	range		1.6−6.2,[k] 3.2−6.8,[k] 6.7−13.4[p]	0.5−40[u] (graph), 3−34[112]	0.5−30,[u] 0.2−1.3[u]
Lipids (mg/mL)					
fasted	median		0.5[k]		
	mean	0.56[p]	0.6[p]	0.1 ± 0.01 mM[q]	
	range		0−1.8[k]		
fed	median		1.8,[k] 2.6[k]		
	mean			22 ± 1 mM[q]	
	range	50 (l),[p] 150 (e)[p]	0.5−4.6,[k] 1.1−3.6,[k] 55−100[p]		
Phospholipids (mM)					
fasted	median		0.6[k]		
	mean			0.2 ± 0.07[q]	
	range		0.1−1.5,[k] 0.03−0.06[r]		
fed	median		1.8,[k] 1.2[k]		
	mean			3 ± 0.3[q]	
	range		1.3−2.4,[k] 0.8−1.6[k]		
Pepsin (mg/mL)					
fasted	median	0.11 (e),[l] 0.22 (m)[l]			
	mean	0.87[w]			
	range	0.83−1.27[x]			
fed	mean	1.25,[w] 1.68[w]			
	range	0.26−0.58,[l] 0.56−1.72[x]			
Lipase					
fasted	mean	∼0.1 mg/mL[y]			
fed	range	11.4−43.9 U/mL[p]			
Potassium (mM)					
fasted	mean	13.4 ± 3.0[j]		5.4 ± 2.1,[j] 4.8 ± 0.5[e]	4.9 ± 1.5[e]
Sodium (mM)					
fasted	mean	68 ± 29[j]		142 ± 13,[j] 142 ± 7[e]	140 ± 6[e]
fed	mean			106 ± 15,[u] 101 ± 17[u]	139 ± 11,[u] 133 ± 8[u]
Chloride (mM)					
fasted	mean	102 ± 28[j]		126 ± 19,[j] 135 ± 8[e]	125 ± 12[e]
Calcium (mM)					
fasted	mean	0.6 ± 0.2[j]		0.5 ± 0.3[j]	

[a] The designation (e) indicates a value that was measured early in the postprandial phase (between 0 and 60 min), (m) denotes a value measured in the mid-postprandial phase, and (l) denotes a value that was measured late in the postprandial phase (greater than 100 min). Unless indicated next to the value, units are noted next to the name of the component. [b] From ref 21. [c] From ref 40. [d] From ref 42. [e] From ref 43. [f] From ref 39. [g] From ref 41. [h] From ref 22. [i] From ref 44. [j] From ref 50. [k] From ref 33. [l] From ref 14. [m] From ref 20. [n] From ref 19. [o] From ref 2. [p] From ref 18. [q] From ref 35. [r] From ref 34. [s] From ref 53. [t] From ref 38. [u] From ref 36. [v] From ref 37. [w] From ref 15. [x] From ref 16. [y] From ref 17.

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 to 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 0.1 mg/mL.[17] Lipase activity in the fed stomach has been shown to range from 11.4 to 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

(17) Vertzoni, M.; Dressman, J.; Butler, J.; Hempenstall, J.; Reppas, C. Simulation of Fasting Gastric Conditions and Its Importance for the in Vivo Dissolution of Lipophilic Compounds. *Eur. J. Pharm. Biopharm.* **2005**, *60*, 413–417.

(18) Armand, M.; Borel, P.; Pasquier, B.; Dubois, C.; Senft, M.; Andre, M.; Peyrot, J.; Salducci, J.; Lairon, D. Physicochemical Characteristics of Emulsions During Fat Digestion in Human Stomach and Duodenum. *Am. J. Physiol.* **1996**, *34*, G172–G183.

(19) Vertzoni, M.; Archontaki, H.; Reppas, C. Determination of Intralumenal Individual Bile Acids by HPLC with Charged Aerosol Detection. *J. Lipid Res.* **2008**, *49*, 2690–2695.

Table 3. Literature Values for Properties of Fluids in the Fasted and Fed Stomach and Small Intestine[a]

		stomach	duodenum	jejunum	ileum
Buffer Capacity (mmol L^{-1} pH^{-1})					
fasted	median	7 (e),[b] 18[b]	5.6[b]		
	mean			3.23[c]	6.4[c]
	range		4−13[d]	2.4−2.8[e]	
fed	range	14−28[b]	18−30[b]	13.2−14.6[e]	
Osmolality (mOsm kg^{-1})					
fasted	median	98 (e),[b] 140 (l)[b]	178,[b] 224[f]		
	mean	29,[g] 191 ± 36,[h] 33.6 ± 5.9,[i] 221 ± 15[i]	142,[g] 137 ± 54[d]	271 ± 15,[h] 200 ± 68,[d] 278 ± 16[i]	
	range	171−276[j]	124−266[f]		
fed	median	559 (e),[b] 217 (l)[b]	287,[f] 276,[f] >287 (e),[b] 287 (l)[b]		
	range		250−367,[f] 268−304[f]		
Surface Tension (mN m^{-1})					
fasted	median		32.3,[b] 41.2[f]		
	mean			28 ± 1,[e] 33.7 ± 2.8[i]	
	range	41.9−45.7[b]	33.3−46.0[f]		
fed	median		34.2[f], 35.4[f]		
	mean			27 ± 1[e]	
	range	30−31[b]	32.2−36.7,[f] 33.7−36.0[f]		
Viscosity (cP)					
fed	range	10−2000[k]			
pH					
fasted	median	1.7,[l] 2.4 (e),[b] 1.7 (l),[b] 1.8[50]	6.2[b], 6.6[f], 5.63[113]	7.2[l]	
	mean	2.9 ± 1.97[h]	6.71 ± 0.44,[m] 7.0 ± 0.4,[d] 4.9,[n] 6.4 ± 0.6[o]	6.8 ± 0.4,[d] 7.5,[e] 7.1 ± 0.60[h]	6.5 ± 0.2[p]
	range	1−2.5,[q] 1.4−2.1,[l] 1.23−7.36,[b] 1.4−7.5[h]	5.8−6.5,[l] 4.00−5.39,[m] 5.17−6.10[o]	4.4−6.5,[114] 5.3−8.1,[l] 5.3−8.1[h]	6.8−8.0[r]
fed	median	5.0,[l] 6.4 (e),[b] 2.7 (l)[b]	5.4,[l] 6.6 (e),[b] 5.2 (l),[b] 5.9,[f] 6.1,[f] 5.35[s]		
	mean		5.2 (e),[n] 4.2 (l)[n]	6.2 ± 0.2 (e),[s] 5.4 ± 0.2 (l),[s] 6.1[e]	7.5[s]
	range	4.3−5.4[l]	3.1−6.7,[l] 4.5−5.5 (e),[n] 3.9−4.8 (l),[n] 5.1−5.7 (e),[114] 5.3−6.1 (l),[114] 4.6−6.3[s]	5.2−6.0 (e)[n]	6.8−7.8,[118] 6.8−8.0[115]

[a] The designation (e) indicates a value that was measured early in the postprandial phase (between 0 and 60 min), (m) denotes a value measured in the mid-postprandial phase, and (l) denotes a value that was measured late in the postprandial phase (greater than 100 min). Unless indicated next to the value, units are noted next to the name of the component. [b] From ref 14. [c] From ref 59. [d] From ref 53. [e] From ref 35. [f] From ref 33. [g] From ref 61. [h] From ref 50. [i] From ref 63. [j] From ref 62. [k] From ref 67. [l] From ref 51. [m] From ref 52. [n] From ref 57. [o] From ref 54. [p] From ref 55. [q] From ref 49. [r] From ref 56. [s] From ref 58.

predominate.[19] Bicarbonate concentrations in the fasted stomach have been shown to range from 7 to 20 mequiv/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 3-fold higher when taken with a high-lipid meal compared with 200 mL of water.[26] However, in some cases

(20) Rhodes, J.; Barnardo, D. E.; Phillips, S. F.; Rovelsta, Ra; Hofmann, A. F. Increased Reflux of Bile into Stomach in Patients with Gastric Ulcer. *Gastroenterology* **1969**, *57*, 241–252.

(21) Kristensen, M. Titration Curves for Gastric-Secretion - Study on Duodenal-Ulcer and Gastric-Ulcer with Particular Reference to Effect of Glycopyrronium. *Scand. J. Gastroenterol.* **1975**, *10*, 1–148.

(22) Rees, W. D.; Botham, D.; Turnberg, L. A. A Demonstration of Bicarbonate Production by the Normal Human Stomach in Vivo. *Dig. Dis. Sci.* **1982**, *27*, 961–966.

(23) Widmaier, E. P.; Raff, H.; Strang, K. T. The Digestion and Absorption of Food. In *Vander's Human Physiology: The Mechanisms of Body Function*, 10th ed.; McGraw-Hill: New York, 2006; pp 575−614.

(24) Konturek, P. C.; Konturek, S. J.; Hahn, E. G. Duodenal Alkaline Secretion: Its Mechanisms and Role in Mucosal Protection against Gastri Acid. *Dig. Liver Dis.* **2004**, *36*, 505–512.

(25) Sheng, J. J.; McNanara, D. P.; Amidon, G. L. Toward an in Vivo Dissolution Methodology: A Comparison of Phosphate and Bicarbonate Buffers. *Mol. Pharmaceutics* **2009**, *6*, 29–39.

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 to 1.8 mg/mL in the fasted and 0.5 to 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 to 0.6 mM in the fasted[33,34] and 0.8 to 3 mM in the fed state.[33,35] Bile salt concentrations have ranged from 0.6 to 17 mM[2,33] and 1.6 to 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 to 10 mM and 0.2 to 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 to 75 mM in the ileum.[39−43] Values in the fed state are less abundant. Rune and co-workers reported a value of 10 mequiv 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

(26) Sunesen, V. H.; Vedelsdal, R.; Kristensen, H. G.; Christrup, L.; Mullertz, A. Effect of Liquid Volume and Food Intake on the Absolute Bioavailability of Danazol, a Poorly Soluble Drug. *Eur. J. Pharm. Sci.* **2005**, *24*, 297–303.
(27) Leyden, J. J. Absorption of Minocycline Hydrochloride and Tetracycline Hydrochloride - Effect of Food, Milk, and Iron. *J. Am. Acad. Dermatol.* **1985**, *12*, 308–312.
(28) Clarysse, S.; Psachoulias, D.; Brouwers, J.; Tack, J.; Annaert, P.; Duchateau, G.; Reppas, C.; Augustijns, P. Postprandial Changes in Solubilizing Capacity of Human Intestinal Fluids for Bcs Class II Drugs. *Pharm. Res.* **2009**, *26*, 1456–1466.
(29) Evans, D. F. Wennerström, H., Micellar Solutions Play a Key Role in Many Industrial and Biological Processes. In *The Colloidal Domain: Where Physics, Chemistry, Biology, and Technology Meet*, 2nd ed.; VCH Publishers Inc.: New York, 1999; pp 198−216.
(30) Rosoff, M.; Serajuddin, A. T. M. Solubilization of Diazepam in Bile-Salts and in Sodium Cholate-Lecithin-Water Phases. *Int. J. Pharm.* **1980**, *6*, 137–146.
(31) Mithani, S. D.; Bakatselou, V.; TenHoor, C. N.; Dressman, J. B. Estimation of the Increase in Solubility of Drugs as a Function of Bile Salt Concentration. *Pharm. Res.* **1996**, *13*, 163–167.
(32) Cai, X. H.; Grant, D. J. W.; Wiedmann, T. S. Analysis of the Solubilization of Steroids by Bile Salt Micelles. *J. Pharm. Sci.* **1997**, *86*, 372–377.
(33) Clarysse, S.; Tack, J.; Lammert, F.; Duchateau, G.; Reppas, C.; Augustijns, P. Postprandial Evolution in Composition and Characteristics of Human Duodenal Fluids in Different Nutritional States. *J. Pharm. Sci.* **2009**, *98*, 1177–1192.
(34) Brouwers, J.; Tack, J.; Lammert, F.; Augustijns, P. Intraluminal Drug and Formulation Behavior and Integration in in Vitro Permeability Estimation: A Case Study with Amprenavir. *J. Pharm. Sci.* **2006**, *95*, 372–383.
(35) Persson, E. M.; Gustafsson, A. S.; Carlsson, A. S.; Nilsson, R. G.; Knutson, L.; Forsell, P.; Hanisch, G.; Lennernas, H.; Abrahamsson, B. The Effects of Food on the Dissolution of Poorly Soluble Drugs in Human and in Model Small Intestinal Fluids. *Pharm. Res.* **2005**, *22*, 2141–2151.
(36) Ladas, S. D.; Isaacs, P. E.; Murphy, G. M.; Sladen, G. E. Comparison of the Effects of Medium and Long Chain Triglyceride Containing Liquid Meals on Gall Bladder and Small Intestinal Function in Normal Man. *Gut* **1984**, *25*, 405–411.
(37) Fausa, O. Duodenal Bile Acids after a Test Meal. *Scand. J. Gastroenterol.* **1974**, *9*, 567–570.
(38) Northfield, T. C.; McColl, I. Postprandial Concentrations of Free and Conjugated Bile Acids Down the Length of the Normal Human Small Intestine. *Gut* **1973**, *14*, 513–518.
(39) McGee, L. C.; Hastings, A. B. The Carbon Dioxide Tension and Acid-Base Balance of Jejunal Secretions in Man. *J. Biol. Chem.* **1942**, *142*, 893–904.
(40) Hardman, J. G. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*, 10th ed.; McGraw-Hill: New York, 2001.
(41) Davenport, H. W. Digestion and Absorption. In *Physiology of the Digestive Tract*; Year Book Medical Publishers, Inc.: Chicago, 1982; pp 179−235.
(42) White, A.; Handler, P.; Smith, E. L. Specialized Extracellular Fluids. In *Principles of Biochemistry*, 4th ed.; McGraw-Hill: New York, 1968; pp 806−827.
(43) Banwell, J. G.; Gorbach, S. L.; Pierce, N. F.; Mitra, R.; Mondal, A. Acute Undifferentiated Human Diarrhea in Tropics 2. Alterations in Intestinal Fluid and Electrolyte Movements. *J. Clin. Invest.* **1971**, *50*, 890–900.
(44) Rune, S. J. Acid-Base Parameters of Duodenal Contents in Man. *Gastroenterology* **1972**, *62*, 533–539.

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 to 6.4.[14,51] An approximation of a typical gastric pH profile as measured by Dressman et al.[51] is shown in Figure 1.

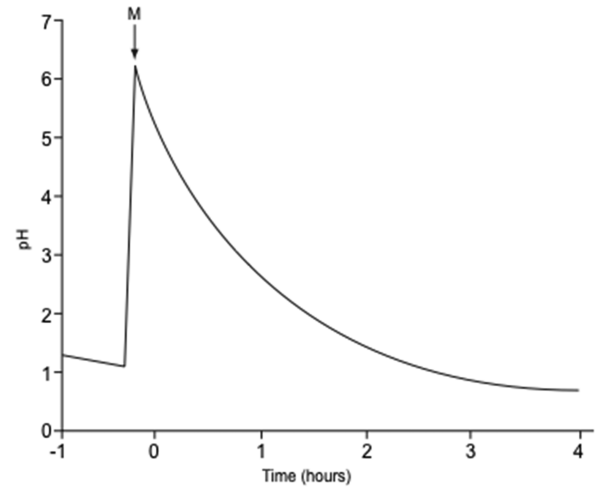

Figure 1. Approximation of a typical pH profile in the stomach. The letter "M" denotes food intake (redrawn from ref 51).

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

(45) Sinko, P. J. Solubility and Distribution Phenomena. In *Martin's Physical Pharmacy*, 5th ed.; Troy, D., Ed.; Lippincott Williams & Wilkins: 2006; pp 231−266.
(46) Sheng, J. J.; Kasim, N. A.; Chandrasekharan, R.; Amidon, G. L. Solubilization and Dissolution of Insoluble Weak Acid, Ketoprofen: Effects of pH Combined with Surfactant. *Eur. J. Pharm. Sci.* **2006**, *29*, 306–314.
(47) Li, S. F.; Wong, S. M.; Sethia, S.; Almoazen, H.; Joshi, Y. M.; Serajuddin, A. T. M. Investigation of Solubility and Dissolution of a Free Base and Two Different Salt Forms as a Function of pH. *Pharm. Res.* **2005**, *22*, 628–635.
(48) Phaechamud, T.; Ritthidej, G. C. Sustained-Release from Layered Matrix System Comprising Chitosan and Xanthan Gum. *Drug Dev. Ind. Pharm.* **2007**, *33*, 595–605.
(49) Evans, D. F.; Pye, G.; Bramley, R.; Clark, A. G.; Dyson, T. J.; Hardcastle, J. D. Measurement of Gastrointestinal pH Profiles in Normal Ambulant Human Subjects. *Gut* **1988**, *29*, 1035–1041.
(50) Lindahl, A.; Ungell, A. L.; Knutson, L.; Lennernas, H. Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women. *Pharm. Res.* **1997**, *14*, 497–502.
(51) Dressman, J. B.; Berardi, R. R.; Dermentzoglou, L. C.; Russell, T. L.; Jarvenpaa, K. M. Upper Gastrointestinal (GI) pH in Young, Healthy Men and Women. *Pharm. Res.* **1990**, *7*, 756–761.
(52) Annaert, P.; Brouwers, J.; Bijnens, A.; Lammert, F.; Tack, J.; Augustijns, P. Ex Vivo Permeability Experiments in Excised Rat Intestinal Tissue and in Vitro Solubility Measurements in Aspirated Human Intestinal Fluids Support Age-Dependent Oral Drug Absorption. *Eur. J. Pharm. Sci.* **2010**, *39*, 15–22.
(53) Perez de la Cruz Moreno, M.; Oth, M.; Deferme, S.; Lammert, F.; Tack, J.; Dressman, J.; Augustijns, P. Characterization of Fasted-State Human Intestinal Fluids Collected from Duodenum and Jejunum. *J. Pharm. Pharmacol.* **2006**, *58*, 1079–1089.
(54) Benn, A.; Cooke, W. T. Intraluminal pH of Duodenum and Jejunum in Fasting Subjects with Normal and Abnormal Gastric or Pancreatic Function. *Scand. J. Gastroenterol.* **1971**, *6*, 313–317.
(55) Youngberg, C. A.; Berardi, R. R.; Howatt, W. F.; Hyneck, M. L.; Amidon, G. L.; Meyer, J. H.; Dressman, J. B. Comparison of Gastrointestinal pH in Cystic-Fibrosis and Healthy Subjects. *Dig. Dis. Sci.* **1987**, *32*, 472–480.
(56) Watson, B. W.; Meldrum, S. J.; Riddle, H. C.; Brown, R. L.; Sladen, G. E. pH Profile of Gut as Measured by Radiotelemetry Capsule. *Br. Med. J.* **1972**, *2*, 104–106.
(57) Ovesen, L.; Bendtsen, F.; Tage-Jensen, U.; Pedersen, N. T.; Gram, B. R.; Rune, S. J. Intraluminal Ph in the Stomach, Duodenum, and Proximal Jejunum in Normal Subjects and Patients with Exocrine Pancreatic Insufficiency. *Gastroenterology* **1986**, *90*, 958–962.
(58) Bown, R. L.; Sladen, G. E.; Clark, M. L.; Dawson, A. M. The Production and Transport of Ammonia in the Human Colon. *Gut* **1971**, *12*, 863.
(59) Fadda, H. M., Sousa, T., Carlsson, A., Abrahamsson, B., Kumar, D. Basit, A. W. In *Drug Solubility in Luminal Fluids from Different Regions of the Small and Large Intestine of Humans*; AAPS Annual Meeting and Exposition, Los Angeles, 2009; p AAPS2009-003733.
(60) Rudolph, M. W.; Klein, S.; Beckert, T. E.; Petereit, H.; Dressman, J. B. A New 5-Aminosalicylic Acid Multi-Unit Dosage Form for the Therapy of Ulcerative Colitis. *Eur. J. Pharm. Biopharm.* **2001**, *51*, 183–190.
(61) Gisolfi, C. V.; Summers, R. W.; Lambert, G. P.; Xia, T. Effect of Beverage Osmolality on Intestinal Fluid Absorption During Exercise. *J. Appl. Physiol.* **1998**, *85*, 1941–8.
(62) Davenport, H. W., Secretion. In *Physiology of the Digestive Tract*; Year Book Medical Publishers, Inc.: Chicago, 1982; pp 101−178.
(63) Pedersen, B. L.; Mullertz, A.; Brondsted, H.; Kristensen, H. G. A Comparison of the Solubility of Danazol in Human and Simulated Gastrointestinal Fluids. *Pharm. Res.* **2000**, *17*, 891–894.

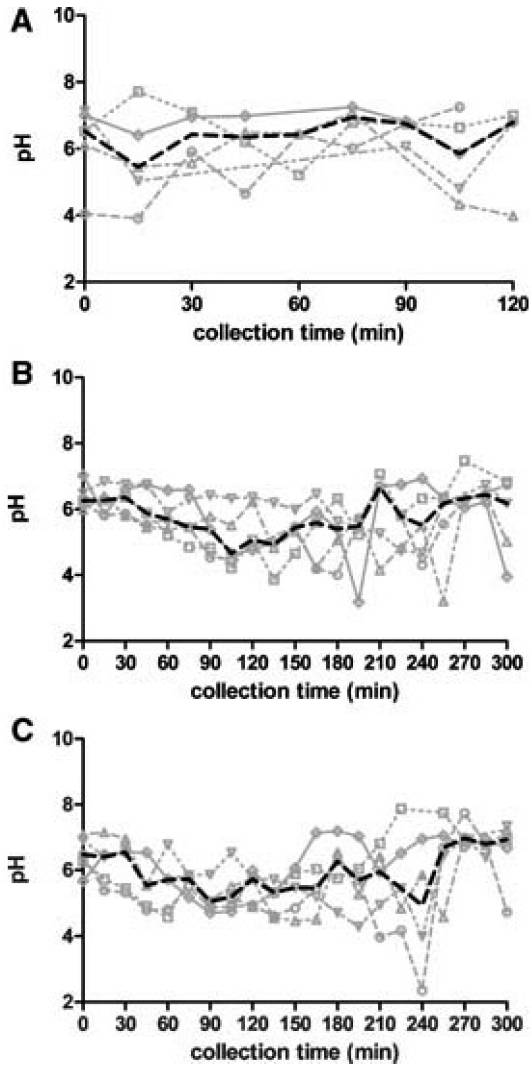

Figure 2. Individual and median pH versus time in fasted (A), fed (B), and fat-enriched fed (C) state human duodenal fluid for five healthy subjects. Darkened lines represent median values.[33] Reprinted with permission from ref 33. Copyright 2009 Wiley-Liss, Inc.

after meal intake and slowly decrease 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 postprandial 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 h 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 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 of Ensure Plus), they found median values of gastric buffer capacity to increase from 14 to 28 mmol L^{-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 to 13 mmol/L/pH in the fasted state,[35,53] and 13 to 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 to 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 to 278 mOsm/kg in the fasted state,[33,63] and 250 to 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 postprandially, 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 to 46 and 30 to 31 mN/m, respectively.[14] In the upper small intestine, surface tension values range from 28 to 46

mN/m in the fasted state, and 27 to 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 (1 cP = 1 mPa s), while 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 co-workers 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. 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 min.[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

(64) Dikeman, C. L.; Fahey, G. C. Viscosity as Related to Dietary Fiber: A Review. *Crit. Rev. Food Sci. Nutr.* **2006**, *46*, 649–663.
(65) Marciani, L.; Gowland, P. A.; Spiller, R. C.; Manoj, P.; Moore, R. J.; Young, P.; Al-Sahab, S.; Bush, D.; Wright, J.; Fillery-Travis, A. J. Gastric Response to Increased Meal Viscosity Assessed by Echo-Planar Magnetic Resonance Imaging in Humans. *J. Nutr.* **2000**, *130*, 122–127.
(66) Dikeman, C. L.; Murphy, M. R.; Fahey, G. C. Dietary Fibers Affect Viscosity of Solutions and Simulated Human Gastric and Small Intestinal Digesta. *J. Nutr.* **2006**, *136*, 913–919.
(67) Abrahamsson, B.; Pal, A.; Sjoberg, M.; Carlsson, M.; Laurell, E.; Brasseur, J. G. A Novel in Vitro and Numerical Analysis of Shear-Induced Drug Release from Extended-Release Tablets in the Fed Stomach. *Pharm. Res.* **2005**, *22*, 1215–1226.
(68) Malkki, Y. Physical Properties of Dietary Fiber as Keys to Physiological Functions. *Cereal Foods World* **2001**, *46*, 196–199.
(69) Lim, C. L.; Byrne, C.; Lee, J. K. W. Human Thermoregulation and Measurement of Body Temperature in Exercise and Clinical Settings. *Ann. Acad. Med. Singapore* **2008**, *37*, 347–353.
(70) Steingoetter, A.; Fox, M.; Treier, R.; Weishaupt, D.; Marincek, B.; Boesiger, P.; Fried, M.; Schwizer, W. Effects of Posture on the Physiology of Gastric Emptying: A Magnetic Resonance Imaging Study. *Scand. J. Gastroenterol.* **2006**, *41*, 1155–1164.
(71) Kwiatek, M. A.; Menne, D.; Steingoetter, A.; Goetze, O.; Forras-Kaufman, Z.; Kaufman, E.; Fruehauf, H.; Boesiger, P.; Fried, M.; Schwizer, W.; Fox, M. R. Effect of Meal Volume and Calorie Load on Postprandial Gastric Function and Emptying: Studies under Physiological Conditions by Combined Fiber-Optic Pressure Measurement and MRI. *Am. J. Physiol.* **2009**, *297*, G894–G901.

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 nondisintegrating 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 50% 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 to 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 retropulsed 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

(72) Schiller, C.; Frohlich, C. P.; Giessmann, T.; Siegmund, W.; Monnikes, H.; Hosten, N.; Weitschies, W. Intestinal Fluid Volumes and Transit of Dosage Forms as Assessed by Magnetic Resonance Imaging. *Aliment. Pharmacol. Ther.* **2005**, *22*, 971–979.

(73) Marciani, L.; Cox, E. F.; Hoad, C. L.; Pritchard, S.; Totman, J. J.; Foley, S.; Mistry, A.; Evans, S.; Gowland, P. A.; Spiller, R. C. Postprandial Changes in Small Bowel Water Content in Healthy Subjects and Patients with Irritable Bowel Syndrome. *Gastroenterology* **2010**, *138*, 469–U90.

(74) Placidi, E., Hoad, C. L., Marciani, L., Gowland, P. A. Spiller, R. C. In *Effects of an Osmotic Laxative on the Distribution of Water between the Small and Large Intestine in Humans*; British Society of Gastroenterology Annual Scientific Meeting, 2010.

(75) Marciani, L., Foley, S., Hoad, C., Campbell, E., Totman, J., Armstrong, A., Manby, P., Gowland, P. A. Spiller, R. In *Effects of Ondansetron on Small Bowel Water Content: A Magnetic Resonance Imaging Study*; United European Gastroenterology Week (UEGW), Paris, 2007.

(76) Sutton, S. C. Role of Physiological Intestinal Water in Oral Absorption. *AAPS J.* **2009**, *11*, 277–285.

(77) Bass, P. Gastric Emptying; Differences among Liquid, Fiber, Polymer and Solid Dosage Forms of Medications. In *Capsugel Symposium Series*; 1993; pp 21−33.

(78) Oberle, R. L.; Chen, T. S.; Lloyd, C.; Barnett, J. L.; Owyang, C.; Meyer, J.; Amidon, G. L. The Influence of the Interdigestive Migrating Myoelectric Complex on the Gastric Emptying of Liquids. *Gastroenterology* **1990**, *99*, 1275–1282.

(79) Dressman, J. B. Comparison of Canine and Human Gastrointestinal Physiology. *Pharm. Res.* **1986**, *3*, 123–131.

(80) Pal, A.; Indireshkumar, K.; Schwizer, W.; Abrahamsson, B.; Fried, M.; Brasseur, J. G. Gastric Flow and Mixing Studied Using Computer Simulation. *Proc. R. Soc. London, Ser. B* **2004**, *271*, 2587–2594.

Table 4. Literature Values for Liquid Volumes and Geometry in the Fasted and Fed Stomach and Small Intestine

			stomach	small intestine
Volume (mL)				
fasted	mean		28[b]	86,[c] 81,[c] 112 ± 27,[d] 109 ± 36,[d]
			296 (300 mL water)[b]	165 ± 22,[e] 105 ± 72[f]
			27[119]	
	range		18−54[b]	34−46[c]
			279−323 (300 mL water)[b]	37−130[c]
			21−33[119]	45−319[f]
fed	mean		250 ± 23 (200 mL),[g] 380 ± 25	47[c]
			(400 mL),[g] 555 ± 30 (600 mL),[f]	381[c]
			664 ± 34 (800 mL)[g]	590 ± 73[d]
				54 ± 41[f]
	range			18−78,[c] 343−491,[c] 20−156[f]
Surface Area (cm^2)				
absorbing	mean		525.58 ± 24.143[120,h], 1100[i]	10^4−1.2 × 10^4 (considering valves of keckring),[120] 10^5 (considering villi),[120] 2 × 10^6 (considering microvilli)[120]
	mean	duodenum		900[i]
		jejunum		600000[i]
		ileum		600000[i]
geometric	mean	942[j]		3300[120]
	mean	duodenum		393[j],
		jejunum		4712[i]
		ileum		4712[i]
	range	duodenum		197−490[k]
		jejunum		825−1319[k]
		ileum		980−1862[k]
Length (cm)[120,l]				
anatomical	mean			680
	range			255−1128
	mean	jejunum		260
		ileum		395
	range	duodenum		25−30
physiological	mean			282
	range			229−337
	mean	duodenum		21
		jejunum		105
		ileum		156
	range	duodenum		18−26
Diameter (cm)				
absolute	mean	duodenum	15[h]	5[i], 4[120]
		jejunum		5[i]
		ileum		5[i]
	range	duodenum		3.5−6[120]
		jejunum		2.5−4[120]
		ileum		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] Values for the small intestine are for the entire small intestine unless otherwise noted. [b] From ref 70. [c] From ref 73. [d] From ref 74. [e] From ref 75. [f] From ref 72. [g] From ref 71. [h] Surface area of gastric mucosa. [i] From ref 95. [j] Calculated using length and diameter from ref 95 assuming cylindrical geometry. [k] Calculated using absolute diameter and physiological length from ref 120 assuming cylindrical geometry. [l] 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[a]

condition		fasted	fed
total vol of liquid (mL)	mean ± SD	105 ± 72[b]	54 ± 41[b]
	range	45−319	20−156
	median	83	39
	individual (approx)[c]	45, 48, 69, 73, 77, 81, 85, 94, 113, 115, 130, 319	20, 22, 26, 28, 30, 38, 44, 50, 70, 75, 101, 156
no. of liquid pockets	mean	4[d]	6[d]
	individual (approx)[c]	2, 3, 4, 5, 8	2, 5, 6, 7, 11
vol of liquid pocket (ml)	median	12[e]	4[e]
no. of capsules surrounded by liquid	no./total	14/28	1/5
no. of capsules partially surrounded by liquid	no./total	6/28	1/5
no. of capsules not in contact with liquid	no./total	8/28	3/5

[a] Reproduced from ref 72. Fasting conditions and 1 h after a meal ($n = 12$).[72] [b] $P < 0.01$. [c] Approximate values read from graph. [d] $P < 0.05$. [e] $P < 0.001$.

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 (300 mL of water),[a] 12 (saline),[b] 75 (glucose)[c]
	range	11.5−17.0 (300 mL 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]
Transit Time—Duodenum to Jejunum (min)[123]		
fed	mean	32 ± 3 (40 kcal/h), 30 ± 1 (90 kcal/h), 32 ± 2 (160 kcal/h)
Transit Time—Duodenum to Ileum (min)[123]		
fed	mean	59 ± 2 (160 kcal/h), 47 ± 3 (40 kcal/h), 47 ± 2 (90 kcal/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 ref 70. [b] From ref 85. [c] From ref 79. [d] From ref 73. [e] From ref 10. [f] From ref 92. [g] From ref 49. [h] From ref 93.

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]

(81) Indireshkumar, K.; Brasseur, J. G.; Faas, H.; Hebbard, G. S.; Kunz, P.; Dent, J.; Feinle, C.; Li, M. J.; Boesiger, P.; Fried, M.; Schwizer, W. Relative Contributions Of "Pressure Pump" And "Peristaltic Pump" To Gastric Emptying. *Am. J. Physiol.* **2000**, *278*, G604–G616.

(82) Pal, A.; Williams, R. B.; Cook, I. J.; Brasseur, J. G. Intrabolus Pressure Gradient Identifies Pathological Constriction in the Upper Esophageal Sphincter During Flow. *Am. J. Physiol.* **2003**, *285*, G1037–G1048.

(83) Pal, A.; Brasseur, J. G.; Abrahamsson, B. A Stomach Road Or "Magenstrasse" For Gastric Emptying. *J. Biomech.* **2007**, *40*, 1202–1210.

(84) Higaki, K.; Choe, S. Y.; Lobenberg, R.; Welage, L. S.; Amidon, G. L. Mechanistic Understanding of Time-Dependent Oral Absorption Based on Gastric Motor Activity in Humans. *Eur. J. Pharm. Biopharm.* **2008**, *70*, 313–325.

Table 7. Effects of Meal Volume and Caloric Load on the Half-Emptying Time of Gastric Contents[a]

	meal vol (mL)			
caloric load (kcal)	200	400	600	800
200	56 (7)	41 (8)	42 (8)	38 (8)[b]
300	74 (7)[c]	59 (8)[c]	60 (8)[c]	56 (8)[b,c]
400	92 (7)[c]	77 (8)[c]	78 (8)[c]	74 (8)[b,c]

[a] Reproduced from ref 71. Data and standard error between any 2 volumes (in parentheses) were estimated from mixed-effects model. The standard errors for differences between 2 volumes are given in parentheses.[71] [b] $P \leq 0.05$ vs 200 mL. [c] $P < 0.01$ vs 200 kcal.[71]

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 to 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 to 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 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 co-workers.[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 co-workers 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 nondisintegrating 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 to 5.4 h with a mean of 3.2 h for a single individual

(85) Granger, D. N.; Barrowman, J. A.; Kvietys, P. R. *Clinical Gastrointestinal Physiology*; W. B. Saunders: Philadelphia, 1985.
(86) Rhie, J. K.; Hayashi, Y.; Welage, L. S.; Frens, J.; Wald, R. J.; Barnett, J. L.; Amidon, G. E.; Putcha, L.; Amidon, G. L. Drug Marker Absorption in Relation to Pellet Size, Gastric Motility and Viscous Meals in Humans. *Pharm. Res.* **1998**, *15*, 233–238.
(87) Podczeck, F.; Mitchell, C. L.; Newton, J. M.; Evans, D.; Short, M. B. The Gastric Emptying of Food as Measured by Gamma-Scintigraphy and Electrical Impedance Tomography (EIT) and Its Influence on the Gastric Emptying of Tablets of Different Dimensions. *J. Pharm. Pharmacol.* **2007**, *59*, 1527–1536.
(88) Kamba, M.; Seta, Y.; Kusai, A.; Ikeda, M.; Nishimura, K. A Unique Dosage Form to Evaluate the Mechanical Destructive Force in the Gastrointestinal Tract. *Int. J. Pharm.* **2000**, *208*, 61–70.
(89) Laulicht, B.; Tripathi, A.; Schlageter, V.; Kucera, P.; Mathiowitz, E. Understanding Gastric Forces Calculated from High-Resolution Pill Tracking. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 8201–8206.
(90) Weitschies, W.; Kosch, O.; Monnikes, H.; Trahms, L. Magnetic Marker Monitoring: An Application of Biomagnetic Measurement Instrumentation and Principles for the Determination of the Gastrointestinal Behavior of Magnetically Marked Solid Dosage Forms. *Adv. Drug Delivery Rev.* **2005**, *57*, 1210–1222.

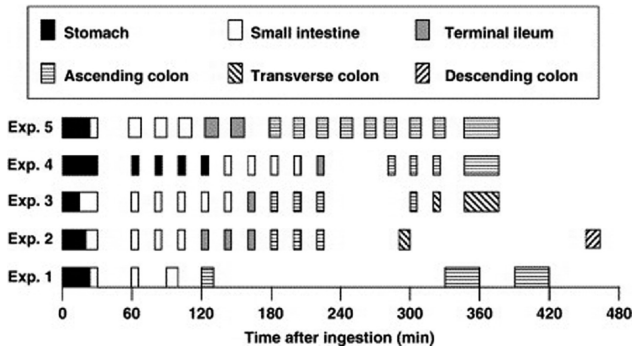

Figure 3. Gastrointestinal transit of magnetically marked nondisintegrating capsules in a single volunteer after ingestion with 150 mL of water. Capsule taken after 8 h of fasting. Lunch served 240 min after ingestion of the capsule in experiments 1−4.[90] Reprinted with permission from ref 90. Copyright 2005 Elsevier B.V.

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 flow rates 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 and 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. Fingerlike 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

(91) Davis, S. S.; Hardy, J. G.; Fara, J. W. Transit of Pharmaceutical Dosage Forms through the Small-Intestine. *Gut* **1986**, *27*, 886–892.

(92) Coupe, A. J.; Davis, S. S.; Wilding, I. R. Variation in Gastrointestinal Transit of Pharmaceutical Dosage Forms in Healthy-Subjects. *Pharm. Res.* **1991**, *8*, 360–364.

(93) Kerlin, P.; Zinsmeister, A.; Phillips, S. Relationship of Motility to Flow of Contents in the Human Small-Intestine. *Gastroenterology* **1982**, *82*, 701–706.

(94) Mayersohn, M., Principles of Drug Absorption. In *Modern Pharmaceutics*; Marcel Dekker: New York, 1996; pp 21−71.

(95) Grassi, M., Grassi, G., Lapasin, R. Colombo, I., Part 1: Gastrointestinal Tract. In *Understanding Drug Release and Absorption Mechanisms, a Physical and Mathematical Approach*, 1st ed.; CRC Press: Boca Raton, 2007; pp 29−68.

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	sodium taurocholate, 80 μM	sodium chloride, 148 mM	sodium chloride, 237.02 mM	sodium chloride, 122.6 mM
	pepsin, 3.2 g/L	lecithin, 20 μM	milk:buffer, 1:0	acetic acid, 17.12 mM	ortho-phosphoric acid, 5.5 mM
	sodium chloride, 34.2 mM	pepsin, 0.1 mg/mL	hydrochloric acid/ sodium hydroxide, q.s.	sodium acetate, 29.75 mM	sodium dihydrogen phosphate, 32 mM
		sodium chloride, 34.2 mM		milk:buffer, 1:1	milk:buffer, 1:3
		hydrochloric acid, q.s.		hydrochloric acid/sodium hydroxide, q.s.	hydrochloric acid/sodium hydroxide, q.s.

[a] From ref 17. [b] From ref 6.

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 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

(96) USP, *The Pharmacopeia of the United States of America XV*; Mack Publishing Company: Easton, 1955.

(97) Jantratid, E.; De Maio, V.; Ronda, E.; Mattavelli, V.; Dressman, J. B.; et al. Application of Biorelevant Dissolution Tests to the Prediction of in Vivo Performance of Diclofenac Sodium from an Oral Modified-Release Pellet Dosage Form. *Eur. J. Pharm. Sci.* **2009**, *37*, 434–441.

(98) Jung, H.; Milan, R. C.; Girard, M. E.; Leon, F.; Montoya, M. A. Bioequivalence Study of Carbamazepine Tablets: In Vitro in Vivo Correlation. *Int. J. Pharm.* **1997**, *152*, 37–44.

(99) Baxter, J. L.; Kukura, J.; Muzzio, F. J. Hydrodynamics-Induced Variability in the USP Apparatus II Dissolution Test. *Int. J. Pharm.* **2005**, *292*, 17–28.

(100) Baxter, J. L.; Kukura, J.; Muzzio, F. J. Shear-Induced Variability in the United States Pharmacopeia Apparatus 2: Modifications to the Existing System. *AAPS J.* **2005**, *7*, E857−E864.

(101) Kukura, J.; Arratia, P. E.; Szalai, E. S.; Muzzio, F. J. Engineering Tools for Understanding the Hydrodynamics of Dissolution Tests. *Drug Dev. Ind. Pharm.* **2003**, *29*, 231. +.

(102) Kukura, J.; Baxter, J. L.; Muzzio, F. J. Shear Distribution and Variability in the USP Apparatus 2 under Turbulent Conditions. *Int. J. Pharm.* **2004**, *279*, 9–17.

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 (combined 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,	monobasic potassium phosphate, 50.0 mM	sodium taurocholate, 3 mM	sodium taurocholate, 3 mM	sodium taurocholate, 3 mM	sodium taurocholate, 15 mM	sodium taurocholate, 15 mM	sodium taurocholate, 10 mM
	50.0 mM[d]	sodium hydroxide, ~15.4 mM	egg phosphatidylcholine, 0.75 mM	egg phosphatidylcholine, 0.75 mM	lecithin, 0.2 mM	egg phosphatidylcholine, 3.75 mM	egg phosphatidylcholine, 3.75 mM	lecithin, 2 mM
	sodium hydroxide, ~15.4 mM[d]	pancreatin, 10.0 g/L	sodium dihydrogen phosphate, 28.66 mM	maleic anhydride, 25.01 mM	maleic acid, 19.12	acetic acid, 144 mM	citric acid, 84 mM	glyceryl monooleate, 5 mM
	pancreatin, 10.0 g/L	hydrochloric acid/ sodium hydroxide, q.s.	sodium hydroxide, ~13.8 mM	sodium hydroxide, ~45 mM	sodium hydroxide, 34.8 mM	sodium hydroxide, ~101 mM	sodium hydroxide, ~200 mM	maleic acid, 55.02 mM
	hydrochloric acid/ sodium hydroxide, q.s.		sodium chloride, 106 mM	sodium chloride, 109 mM	sodium chloride, 68.62 mM	sodium chloride, 173 mM	sodium chloride, 206 mM	sodium oleate, 0.8 mM
								sodium hydroxide, 81.65 mM
								sodium chloride, 125.5 mM

[a] From ref 127. [b] From ref 128. [c] From ref 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]

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 non-physiological 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

(103) Sjoberg, M.; Laurell, E.; Carlsson, M.; Abrahamsson, B.; Pal, A.; Brasseur, J. G. A New in Vitro Dissolution Method Providing in Vivo Relevant Gastric Shear Stress. *Eur. J. Pharm. Sci.* **2004**, *23*, S45–S45.
(104) Sheng, J. J.; Sirois, P. J.; Dressman, J. B.; Amidon, G. L.; Particle Diffusional Layer Thickness in a Usp Dissolution Apparatus, I. I. A Combined Function of Particle Size and Paddle Speed. *J. Pharm. Sci.* **2008**, *97*, 4815–4829.
(105) Bucher, G. R.; Flynn, J. C.; Robinson, C. S. The Action of the Human Small Intestine in Altering the Composition of Physiological Saline. *J. Biol. Chem.* **1944**, *155*, 305–313.
(106) Repishti, M.; Hogan, D. L.; Pratha, V.; Davydova, L.; Donowitz, M.; Tse, C. M.; Isenberg, J. I. Human Duodenal Mucosal Brush Border Na+/H+ Exchangers Nhe2 and Nhe3 Alter Net Bicarbonate Movement. *Am. J. Physiol.* **2001**, *281*, G159–G163.
(107) West, J. B. Absorption. In *Best and Taylor's Physiological Basis of Medical Practice*, 11th ed.; Williams & Wilkins: Baltimore, 1985; pp 751−790.
(108) Johnson, L. R. Fluid and Electrolyte Absorption. In *Gastrointestinal Physiology*, 6th ed.; Johnson, L. R., Ed.; Mosby: St. Louis, 2001; pp 143−154.
(109) Rune, S. J.; Henriksen, F. W. Carbon Dioxide Tensions in the Proximal Part of the Canine Gastrointestinal Tract. *Gastroenterology* **1969**, *56*, 758–762.
(110) Efentakis, M.; Dressman, J. B. Gastric Juice as a Dissolution Medium: Surface Tension and pH. *Eur. J. Drug Metab. Pharmacokinet.* **1998**, *23*, 97–102.
(111) Rautureau, M.; Bisalli, A.; Rambaud, J. C. Bile Salts and Lipids in Aqueous Intraluminal Phase During the Digestion of a Standard Meal in Normal Man. *Gastroenterol. Clin. Biol.* **1981**, *5*, 417–425.
(112) Tangerman, A.; van Schaik, A.; van der Hoek, E. W. Analysis of Conjugated and Unconjugated Bile Acids in Serum and Jejunal Fluid of Normal Subjects. *Clin. Chim. Acta* **1986**, *159*, 123–132.
(113) Bratten, J.; Jones, M. P. Prolonged Recording of Duodenal Acid Exposure in Patients with Functional Dyspepsia and Controls Using a Radiotelemetry pH Monitoring System. *J. Clin. Gastroenterol.* **2009**, *43*, 527–533.
(114) Maxwell, J. D.; Ferguson, A.; Watson, W. C. The Effect of Gastric Secretory Status on Jejunal pH Measured by Radiotelemetering. *Digestion* **1971**, *4*, 345–352.
(115) Zentler-Munro, P. L.; Fine, D. R.; Fitzpatrick, W. J.; Northfield, T. C. Effect of Intrajejunal Acidity on Lipid Digestion and Aqueous Solbilisation of Bile Acids and Lipids in Health, Using a New Simple Method of Lipase Inactivation. *Gut* **1984**, *25*, 491–499.
(116) Borgstrom, B.; Dahlqvist, A.; Lundh, G.; Sjovall, J. Studies of Intestinal Digestion and Absorption in the Human. *J. Clin. Invest.* **1957**, *36*, 1521–1536.
(117) Malagelada, J. R.; Longstreth, G. F.; Summerskill, W. H. J.; Go, V. L. W. Measurement of Gastric Functions During Digestion of Ordinary Solid Meals in Man. *Gastroenterology* **1976**, *70*, 203–210.
(118) Fordtran, J. S.; Locklear, T. W. Ionic Constituents and Osmolality of Gastric and Small-Intestinal Fluids after Eating. *Am. J. Dig. Dis.* **1966**, *11*, 503–521.
(119) Lobo, D. N.; Hendry, P. O.; Rodrigues, G.; Marciani, L.; Totman, J. J.; Wright, J. W.; Preston, T.; Gowland, P.; Spiller, R. C.; Fearon, K. C. H. Gastric Emptying of Three Liquid Oral Preoperative Metabolic Preconditioning Regimens Measured by Magnetic Resonance Imaging in Healthy Adult Volunteers: A Randomised Double-Blind, Crossover Study. *Clin. Nutr.* **2009**, *28*, 636–641.
(120) Snyder, W. S., Cook, M. J., Nasset, E. S., Karhausen, L. R., Howells, G. P. Tipton, I. H. Anatomical Values for Reference Man. In *Report of the Task Group on Reference Man*; Pergamon Press: New York, 1975; pp 8−46.
(121) Coleman, N. S.; Marciani, L.; Blackshaw, E.; Wright, J.; Parker, M.; Yano, T.; Yamazaki, S.; Chan, P. Q.; Wilde, K.; Gowland, P. A.; Perkins, A. C.; Spiller, R. C. Effect of a Novel 5-Ht3 Receptor Agonist Mkc-733 on Upper Gastrointestinal Motility in Humans. *Aliment. Pharmacol. Ther.* **2003**, *18*, 1039–1048.
(122) Marciani, L.; Gow land, P. A.; Spiller, R. C.; Manoj, P.; Moore, R. J.; Young, P.; Fillery-Travis, A. J. Effect of Meal Viscosity and Nutrients on Satiety, Intragastric Dilution, and Emptying Assessed by MRI. *Am. J. Physiol.* **2001**, *280*, G1227–G1233.
(123) Holtmann, G.; Kelly, D. G.; Sternby, B.; DiMagno, E. P. Survival of Human Pancreatic Enzymes During Small Bowel Transit: Effect of Nutrients, Bile Acids, and Enzymes. *Am. J. Physiol.* **1997**, *273*, G553–G558.
(124) Anwar, S.; Fell, J. T.; Dickinson, P. A. An Investigation of the Disintegration of Tablets in Biorelevant Media. *Int. J. Pharm.* **2005**, *290*, 121–127.
(125) Galia, E.; Nicolaides, E.; Horter, D.; Lobenberg, R.; Dressman, J. B. Evaluation of Various Dissolution Media for Predicting in Vivo Performance of Class I and II Drugs. *Pharm. Res.* **1998**, *15*, 698–705.
(126) Vertzoni, M.; Fotaki, N.; Kostewicz, E.; Stippler, E.; Leuner, C.; Nicolaides, E.; Dressman, J.; Reppas, C. Dissolution Media Simulating the Intralumenal Composition of the Small Intestine: Physiological Issues and Practical Aspects. *J. Pharm. Pharmacol.* **2004**, *56*, 453–462.
(127) USP. *The Pharmacopeia of the United States of America XVI*; Mack Publishing Company: Easton, 1960.
(128) Gray, V. A.; Dressman, J. B. Change of pH Requirements for Standard Intestinal Fluid TS. *Pharmacopeial Forum* **1996**, *22*, 1943–1945.

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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