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Review

Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms

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Dissolution tests are used for many purposes in the pharmaceutical industry: in the development of new products, for quality control and, to assist with the determination of bioequivalence. Recent regulatory developments such as the Biopharmaceutics Classification Scheme have highlighted the importance of dissolution in the regulation of post-approval changes and introduced the possibility of substituting dissolution tests for clinical studies in some cases. Therefore, there is a need to develop dissolution tests that better predict the *in vivo* performance of drug products. This could be achieved if the conditions in the gastrointestinal tract were successfully reconstructed *in vitro*. The aims of this article are, first, to clarify under which circumstances dissolution testing can be prognostic for *in vivo* performance, and second, to present physiological data relevant to the design of dissolution tests, particularly with respect to the composition, volume, flow rates and mixing patterns of the fluids in the gastrointestinal tract. Finally, brief comments are made in regard to the composition of *in vitro* dissolution media as well as the hydrodynamics and duration of the test.

KEY WORDS: dissolution tests; prediction of *in vivo* performance; dissolution test conditions; composition of dissolution media.

INTRODUCTION

An important aspect of the development of a pharmaceutical product is to find an *in vitro* characteristic of potential formulations that reflects their *in vivo* performance. Although immediate release solid dosage forms are routinely subjected to tests such as content uniformity, weight, hardness, friability and disintegration, the test that is most often associated with the assessment of *in vivo* performance is the dissolution test. Currently there are about 500 tablet and capsule monographs in the USP which have dissolution requirements (1), and dissolution testing is an integral component of new drug applications to regulatory bodies worldwide.

In vitro dissolution testing provides useful information at several stages of the drug development process. Formulation scientists use dissolution to assess the dissolution properties of the drug itself and thereby select appropriate excipients for the formulation. Dissolution testing is also employed to assist in choosing among candidate formulations, with the aim of selecting the dosage form with the most suitable and reproducible release profile. However, if these tests are not performed under appropriate conditions, the prediction of which drugs and which dosage forms will exhibit the desired release profiles *in vivo* may be completely erroneous.

Clinical scientists rely on dissolution tests to establish *in vitro/in vivo* correlations between release of drug from the dosage form and drug absorption. When *in vitro* results fail to adequately predict the *in vivo* performance of a drug product, more and larger clinical studies are needed to assess product bioavailability, thus adding substantially to the cost of product development. For drugs and formulations that have release rate limited absorption, it is also of particular interest to know whether the drug will be better absorbed when the product is given with food. Current pharmacopeial tests do not address this need.

From the regulatory scientist's point of view, the evaluation of preclinical and clinical data would be greatly facilitated by the availability of validated, prognostic dissolution methodology for the product. In certain cases, it may be appropriate to use dissolution test results to evaluate the biopharmaceutical implications of a product change, rather than to automatically require a bioequivalence study (2).

Important aspects of the quality assurance of a drug product include the ability to confirm that the correct manufacturing procedures have been followed for a given batch, that batch-to-batch reproducibility of the product meets regulatory requirements, and that the product performs adequately throughout its

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shelf life. Insofar as possible, the *in vitro* test conditions should bear a meaningful relationship to the conditions in the gastrointestinal tract (3). In the case of very poorly soluble drugs, however, the ability to test whether the product is able to release all of the active drug within the desired time-frame under physiologically relevant test conditions may be difficult to achieve with current apparatus.

In summary, there is a real need to develop dissolution tests that better predict *in vivo* performance of drug products. This could be achieved if the conditions in the gastrointestinal tract were successfully reconstructed in *in vitro* test systems. The development of prognostic *in vitro* tests should lead not only to a reduction in the work needed for formulation development, but also in the number and size of clinical studies required, and to more meaningful quality assurance tests.

In this article, we seek first to clarify under which circumstances dissolution testing can be prognostic for *in vivo* performance, then to present physiological data relevant to the design of dissolution tests, particularly with respect to the composition of the medium, the hydrodynamics employed and the duration of the test. In a companion article, examples of drugs for which dissolution is highly dependent on test conditions will be used to illustrate the importance of selecting physiologically relevant test conditions for *in vitro* performance tests.

RATE LIMITING FACTORS TO DRUG ABSORPTION

Essentially, there are four possible sources of incomplete drug absorption following the oral administration of a solid dosage form (4):

1) The drug is not delivered from its formulation over an appropriate time frame in solution form to those sites in the GI tract where it is well absorbed,

2) The drug is decomposed in the gastrointestinal tract or forms a nonabsorbable complex,

3) The drug is not transported efficiently across the gut wall in the apical to basal direction, and/or

4) The drug is metabolized and/or eliminated *en route* to the systemic circulation. These possibilities are illustrated in Figure 1.

Since the gastrointestinal tract is not a static system, the rate at which release, decomposition, complexation and gut wall transport occur must additionally be weighed against the transit rate of the dosage form/drug through the gastrointestinal tract. In order for a drug to be well absorbed, release and uptake must be completed within the time taken for the dosage form/drug to traverse that part of the gastrointestinal tract up to and including the sites at which the drug is absorbed, whereas decomposition and complexation must occur more slowly than either release/uptake or transit.

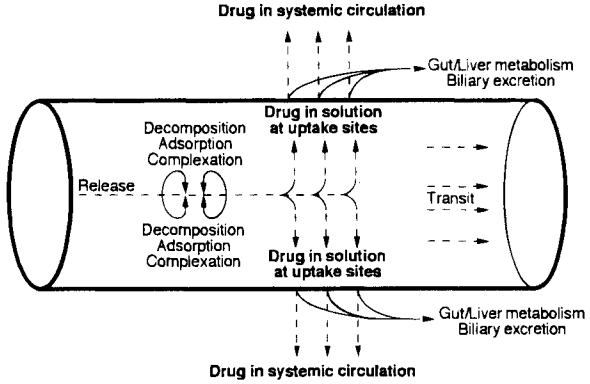

Fig. 1. Steps in drug absorption and sources of incomplete bioavailability following oral administration of a solid dosage form.

THE BIOPHARMACEUTICS CLASSIFICATION SCHEME

Recently, a Biopharmaceutics Classification Scheme (BCS) has been proposed (5). Under this scheme (Table 1), drugs can be categorized into four basic groups according to their solubility properties and their ability to penetrate the gastrointestinal mucosa.

Thus, the BCS addresses two of the potential four limitations to oral drug bioavailability. Of these two, drug solubility recognizes the physicochemical limitations of the drug as a potential source of incomplete release from the dosage form. It is important to understand that the classification is based on the solubility properties of the drug substance throughout the upper GI tract. In the Commentary Section, appropriate media for such studies are suggested. The results of dissolution studies with the drug in the same media can be subsequently used in the development process to assess the influence of formulation on the release rate. Permeability studies are needed to locate the main sites of drug absorption in the gastrointestinal tract, as well as assessing the efficiency of drug transport across the gut wall. A variety of cell culture, tissue and animal models are available for assessing permeability; currently there are also several groups studying permeability of drugs directly in humans (6,7). In principle, studies addressing drug stability problems in the lumen of the gastrointestinal tract should be run in media that reproduce the conditions to which the drug is likely to be subjected. In this respect, considerations for design of stability test media parallel those applicable to release and dissolution studies. In the case of drugs that undergo metabolism in the gut wall and/or liver, the rate and extent of the effect must be assessed using tissue preparations or from pharmacokinetic analysis.

Although the BCS is limited to two of the four important factors, it nonetheless provides a useful starting point for recognizing when and how dissolution tests can aid in the design and evaluation of oral dosage forms. Compounds belonging to Class I, i.e. compounds with high solubility and permeability, should go into solution quickly when they are housed in immediate release dosage forms, and also be rapidly transported across

Table 1. The Biopharmaceutics Classification Scheme

Class I:	**Class II:**
HIGH SOLUBILITY	LOW SOLUBILITY
HIGH PERMEABILITY	HIGH PERMEABILITY
Class III:	**Class IV:**
HIGH SOLUBILITY	LOW SOLUBILITY
LOW PERMEABILITY	LOW PERMEABILITY

Note: From Ref. 5.

the gut wall. Therefore, it is expected that they will be well absorbed unless they are unstable, form insoluble complexes, are secreted directly from the gut wall, or undergo first pass metabolism. Dissolution tests for immediate release formulations of Class I drugs, therefore, need only to verify that the drug is indeed rapidly released from the dosage form under mild aqueous conditions.

For Class II drugs, by contrast, the rate of dissolution of the drug is almost certain to be the principal limitation to its oral absorption. The limitation can be equilibrium or kinetic in nature. In the case of an 'equilibrium' problem there is not enough fluid available in the gastrointestinal tract to dissolve the dose. This can be checked by calculating the dose:solubility ratio (8). For example, at a dose of 500 mg and an aqueous solubility of 15 μg/ml at 37° C, 33 liters of fluid are required to dissolve one dose of griseofulvin. Since the total volume of fluid entering the gastrointestinal tract in a twenty-four hour period is only about five to ten liters (9), there is clearly insufficient volume present at any given time for the entire dose of griseofulvin to be dissolved. In the case of a 'kinetic' problem, the drug dissolves too slowly for the entire dose to become dissolved before the drug has passed by its sites of uptake. Digoxin, for example, with a dose of 0.25 mg and a solubility of 20 μg/ml, has a dose:solubility ratio of just 12.5 ml. Despite the small volume of fluids required to dissolve the drug, digoxin exhibits dissolution rate limited absorption at particle sizes of greater than 10μ in diameter (8) because the poor driving force for dissolution supplied by the solubility, combined with the low surface area of drug at larger particle sizes, is insufficient to ensure timely dissolution. For Class II drugs, it should therefore be possible to establish a strong correlation between the results of dissolution tests and the *in vivo* absorption rate. Establishment of an *in vitro/in vivo* correlation and the resultant ability to discriminate between formulations with different bioavailabilities will be dependent on how well the *in vitro* tests are designed. In order to be successful, it is necessary to reproduce the conditions extant in the gastrointestinal tract following administration of the dosage form as closely as possible. Adequate comparison of formulations for Class II drugs requires dissolution tests with multiple sampling times in order to characterize the release profile (2), and in some cases the use of more than one dissolution medium may also be worth considering.

Like compounds belonging to Class I, Class III drugs are rapidly dissolving and the test criterion should be that the formulation can release the drug under mild aqueous conditions within a predetermined time. Rapid dissolution is particularly desirable for Class III drugs, in order to maximize the contact time between the dissolved drug and the absorbing mucosa, and consequently the bioavailability of the compound. Therefore, the duration of the dissolution test should be at least as stringent for Class III drugs as for Class I drugs. Class IV drugs are expected to have poor absorption in general, but it is anticipated that, as in the case of Class II drugs, poor formulation could have an additional, negative influence on both the rate and extent of drug absorption. Thus, for all four categories, it is anticipated that well-designed dissolution tests can be a key prognostic tool in the assessment of both the drug's potential for oral absorption and of the bioequivalence of its formulations.

IMPORTANT CONSIDERATIONS IN DISSOLUTION AND THEIR CORRESPONDING PHYSIOLOGICAL PARAMETERS

From the following equation, based on the Nernst-Brunner and Levich modifications of the Noyes-Whitney model (10–12), the factors important to the kinetics of drug dissolution can be identified:

$$\frac{dX_d}{dt} = \frac{A * D}{\delta} * (C_s - X_d/V)$$

where A is the effective surface area of the solid drug, D is the diffusion coefficient of the drug, δ is the effective diffusion boundary layer thickness adjacent to the dissolving surface, C_s is the saturation solubility of the drug under lumenal conditions, X_d is the amount of drug already in solution and V is the volume of the dissolution medium. Some of these factors are primarily influenced by physicochemical properties of the drugs, but most are also influenced by the conditions in the gastrointestinal tract. A summary of the relevant physicochemical and physiological parameters is given in Table 2.

The key factors in the dissolution of drugs in the gastrointestinal tract are thus the composition, volume and hydrodynamics of the contents in the lumen following administration of the dosage form. Only when these factors are adequately reproduced *in vitro* can we expect to accurately predict dissolution limitations to absorption.

In addition to these factors, the permeability of the gut wall to the compound plays a role in the maintenance of sink (less than 20% of saturation concentration) conditions for dissolution, which are required for the fastest possible dissolution rate. For highly permeable drugs sink conditions are likely to be maintained, in which case the dissolution rate per unit surface area will be constant and close to the initial dissolution rate. For less permeable drugs, the dissolution rate per unit surface area will decrease with time, due to the gradual buildup of drug in solution in the lumen.

The lumenal conditions in the gastrointestinal tract vary widely both within and between subjects. Intersubject variabil-

Table 2. Physicochemical and Physiological Parameters Important to Drug Dissolution in the Gastrointestinal Tract

Factor	Physicochemical parameter	Physiological parameter
Surface area of drug	particle size, wettability	surfactants in gastric juice and bile
Diffusivity of drug	molecular size	viscosity of lumenal contents
boundary layer thickness		motility patterns & flow rate
Solubility	hydrophilicity, crystal structure, solubilization	pH, buffer capacity, bile, food components
Amount of drug already dissolved		permeability
Volume of solvent available		secretions, coadministered fluids

ity arises from normal genetic variation in the population (as in the case of heart rate, liver function and other physiological parameters) as well as from disease states implicating the gastrointestinal tract. Intrasubject variability may occur as the result of circadian rhythm, food ingestion, physical activity level and stress level, among others. This variability notwithstanding, the remainder of this Section is devoted to a summary of representative values for key parameters in the fed and fasted states in different segments of the gastrointestinal tract.

Lumenal composition in the GI tract

In addition to food and beverages ingested with the dosage form, various fluids are secreted by the gastrointestinal tract, including hydrochloric acid, bicarbonate, enzymes, surfactants, electrolytes, mucus and, of course, water. Thus, parameters that can profoundly influence the solubility and dissolution rate of a drug, e.g. pH, buffer capacity, presence of surfactant concentration and volume of lumenal contents, may vary widely with position in the gastrointestinal tract and with timing of administration of the drug in relation to meal intake.

pH

Values of gastric pH in the fasted state can fluctuate on a minute-to-minute basis over the range pH 1 to pH 7, but in healthy, young Caucasians gastric pH lies below pH 3 during 90% of the fasted state (13), with an interquartile range of pH 1.4 to pH 2.1. Suitable dissolution media for simulating the fasted state gastric conditions will therefore have pH values between pH 1.5 and pH 2. Fasted state gastric pH values of pH 6 and higher are found in two significant subpopulations: those receiving gastric acid blocker therapy and those over the age of 65 years (about 10–20 % of North Americans (14) and Europeans (15) acquire hypo/achlorhydria; the incidence appears to be much higher in Japan (16)). With ingestion of a meal, the gastric juice is initially buffered to a less acidic pH, which is dependent on the meal composition. Typical gastric pH values immediately following meal ingestion are in the range pH 3 to pH 7. Depending on meal size, the gastric pH returns to fasted state values within two to three hours. Thus, only dosage forms ingested with or soon after meal intake will encounter elevated gastric pH under normal physiological circumstances.

Intestinal pH values (Table 3) are considerably higher than gastric pH values due to the neutralization of incoming acid with bicarbonate ion secreted by the pancreas. Furthermore, there is a pH gradient in the small intestine, with values gradually rising between the duodenum and ileum. pH values in the colon are heavily influenced by products of bacterial exoenzyme reactions. Undigested carbohydrate that is passed into the colon is converted into short chain fatty acids (C_2–C_4) that lower the local pH value to around pH 5 (18). Thus, when suitable carbohydrate substrates are present, the pH in the proximal colon may be 2–3 pH units lower than in the terminal ileum.

Table 3. pH in the Small Intestine in Healthy Humans in the Fasted and Fed States[a]

Location	fasted state pH	fed state pH
mid-distal duodenum	4.9	5.2
	6.1	5.4
	6.3	5.1
	6.4	
jejunum	4.4–6.5	5.2–6.0
	6.6	6.2
ileum	6.5	6.8–7.8
	6.8–8.0 (range)	6.8–8.0
	7.4	7.5

[a] Reproduced from Ref. 17, which summarized results from several studies in the literature.

Table 4. Comparison of Average pH and Buffer Capacity of Chyme Recovered at Midgut From Fistulated Dogs, After Administration of Nonnutrient and Nutrient 'Meals', with Those of Simulated Intestinal Fluid USP, Without Pancreatin

Sample	pH	Buffer capacity (mEq/L/pH unit)
Nonnutrient 'meal' (water)	6.0[a]	0.16 ± 0.16[b]
Nutrient meal (cheeseburger, fries, water)	5.2[a]	76 ± 25[b]
SIFsp (USP)*	7.5	25.8 ± 0.8

Note: Excerpted from Ref. 20.
Shared letters indicate significant differences, [a]$p < 0.05$, [b]$p < 0.005$.
* SIFsp was prepared according to the USP, but without pancreatin. At the time the studies were initiated, the official pH of the medium was 7.5.

Buffer Capacity

The microclimate pH in the diffusion boundary layer adjacent to the dissolving surface is an important determinant to the dissolution of ionizable drugs. In addition to the intrinsic solubility and ionization constant of the drug and the pH of the medium, the buffer capacity of the medium plays an important role in determining the microclimate pH (19). Data obtained in a fistulated dog model (20) suggest that the buffer capacity at midgut is far greater after a cheeseburger/fries/water meal than following administration of water (Table 4).

Surfactants

The surface tension of gastric fluid is considerably lower than that of water, suggesting the presence of surfactants in this region. Usual values in the fasted state lie between 35 and 45 $mN.m^{-1}$ (21). In the small intestine, secretion of bile results in substantial concentrations of bile salts and lecithin, which form mixed micelles even at fasted state concentrations.

Fasting bile salt concentrations of about 3–5 mM have been reported for the proximal small intestine (Table 5). Although

Table 5. Fasting Bile Salt Concentrations in the Human Small Intestine[a]

statistic	duodenum	upper jejunum	lower jejunum
mean ± s.d. (mM)	6.4 ± 1.3 4.3 ± 1.2	5	6
median		3	5
range		0–14	0–17

[a] Data from Refs. 22–25.

Table 6. Postprandial Bile Salt Concentrations in the Human Small Intestine

Time	Location	Statistic	Reference Number
0–30 min	duodenum	mean 14.5 ± 9.4	29
		range 5.8–39.6	
	upper jejunum	mean 16.2 ± 1.5	30
		mean 15	23
		range 4–34	
30–60 min	duodenum	mean 5.2 ± 2.3	29
	upper jejunum	mean 9.7 ± 1	30
		mean 8	23
		range 3–17	
120–150 min	upper jejunum	mean 6.5 ± 0.9	30

concentrations vary widely between individuals, average values are similar in the duodenum and jejunum. Levels fall rapidly in the ileum where bile salts are absorbed by an active transport mechanism, and are insignificant in the colon in healthy individuals.

After eating, the bile output and lumenal concentration of bile components (Table 6) peak within thirty minutes (26). Thereafter levels gradually decline, mostly because of dilution with chyme. The peak level averages about 15 mM in the proximal small intestine. Since the gallbladder empties into the upper small intestine, duodenal levels tend to fluctuate more with meal ingestion than levels in the distal small intestine (27,28).

Enzymes

The primary enzyme found in gastric juice is pepsin, an exopeptidase. Lipases, amylases and proteases (Table 7) are secreted from the pancreas (31) into the small intestine in response to meal ingestion; these enzymes are responsible for the bulk of nutrient digestion. Pepsin and the pancreatic proteases pose a particular threat to stability of proteins and peptides in the lumen, while lipases may affect release of drugs from fat/oil containing dosage forms.

Bacteria, which mainly populate the distal ileum and the colon, also secrete diverse enzymes. Table 8 (32) illustrates some of the enzymes available, classified according to the reactions that they catalyze. The ability of bacterial exoenzymes to split certain chemical bonds has been used to design dosage forms intended for colonic delivery, such as azo polymers and some hydrogels (33–35).

Volume

The volume of fluids available in the gastrointestinal tract for drug dissolution is dependent upon the volume of coadministered fluids, secretions and water flux across the gut wall. About 2 liters per day are ingested orally, though this varies considerably with climate, body weight, activity and personal habit (9). The volume of the stomach in the fasted state may be as little as 20–30 mL, mostly present as wet mucus rather than as a fluid pool. At the other extreme, gastric pressure starts to rise when a volume of about 1.5 liters is exceeded (36).

The secretions of the para-gastrointestinal organs (salivary glands, liver, pancreas) as well as the secretion of the stomach, are received by the first portion of the duodenum. These endogenous secretions, totalling about 6 liters per day, are essential for the normal lumenal digestion of foodstuffs. Approximately 1–2 L of pancreatic juice are secreted into the duodenum over a 24 hour period (37) while bile output in a 24 hour period totals about 600 mL. Most of the pancreatic and biliary output is secreted postprandially. In addition, the intestine secretes about 1 liter of water per day, mostly as a component of mucus.

According to the perfusion studies of Dillard et al. (38), the volume of fluid in the jejunum and ileum varies from 120–350 mL, depending on the perfusion rate. In a landmark study by Fordtran and Locklear (39) (Figure 2), electrolyte and volume measurements were compared at different sites within the small intestine after ingestion of hypertonic (milk/doughnuts) and hypotonic (steak and water) meals. Volumes were considerably higher following administration of a hypertonic meal than after administration of a hypotonic meal. In the case of a hypertonic meal, net water efflux across the mucosa into the lumen occurs due to the osmotic pressure difference, while in the case of a hypotonic meal, there is net water absorption from the meal.

Table 7. Characteristics of Some Exocrine Pancreatic Enzymes

(pro)enzyme	% output	substrates	products
trypsin(ogen)	33	proteins/polypep	peptides, amino acids
chymotrypsin(ogen)	16	proteins/polypep	peptides, aminoacids
(pro)carboxypeptidase A	12	proteins/polypep	amino acids
(pro)carboxypeptidase B	9	proteins/polypep	amino acids
(pro)elastase	8	proteins/polypep	amino acids
ribonucleases	1	nucleic acids	mono-nucleotides
lipase 1	8.5	triglycerides	fatty acids monoglycerides
lipase 2	3.4	triglycerides	monoglycerides
amylase	3.6	polysaccharides	disaccharides trisaccharides limit dextrins

Note: Excerpted from Ref. 31.

Table 8. Bacterial Flora in the Colon and Their Exoenzymes

Bacteria	Reductive Reactions	Hydrolytic Reactions
Bacteroides	nitroreductase	
Clostridia	azoreductase	glucosidase
	hydrogenase	sulfatase
Enterobacteria	nitroreductase	esterase, amidase
	N-oxide-reductase	glucuronidase
	sulfoxide-reductase	sulfatase
Lactobacilli	azoreductase	
	hydrogenase	

Note: Reproduced with permission from Ref. 32.

Fluid levels tend to be lower at more distal locations. Only about 1.5 liters are presented to the colon daily, of which about 1.3 liters are absorbed, with the rest forming a component of the stool (40).

Hydrodynamics in the GI Tract

Mixing Patterns in the Gut

The hydrodynamics in the gastrointestinal tract, that is, how well the lumenal contents are mixed, play an important role in dissolution through their influence on the effective boundary layer thickness, δ. In the upper GI tract, there are basically four motility patterns: no activity (quiescence), segmental movements, propagative movements (short or long range) and tonic contractions (41).

In the fasting stomach, long periods of little or no motor activity occur. About once every two hours, contractions start to occur which gradually become more frequent and more forceful, until they culminate in a burst of activity that clears the contents of the stomach into the intestine (so-called Phase III activity). The quiescent phase can, of course, be modelled by a stagnant system. To date, however, no useful quantitative model of the hydrodynamics of the stomach in the more active phases of the fasted state or in the fed state pattern has been developed.

As far as the small intestine is concerned, some data is available regarding the ratio of segmental to propagative motility as a function of the fed and fasted states. Segmentation is

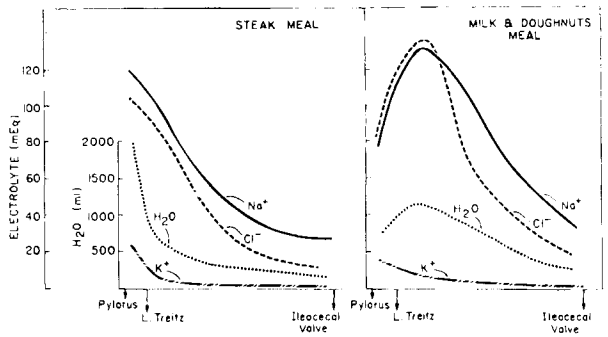

Fig. 2. Water volumes and electrolyte concentrations in the small intestine following ingestion of a hypotonic steak/water meal (Panel A), and a hypertonic milk/doughnuts meal (Panel B). (Reproduced with permission from Ref. 39).

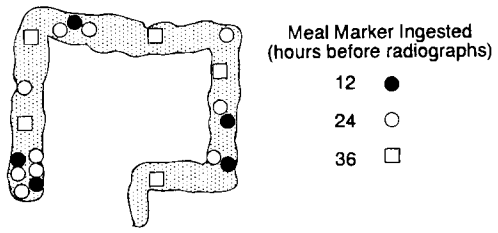

Fig. 3. Distribution of markers in the colon after administration at 12 hour intervals. (Reproduced with permission from Ref. 43).

the predominant mixing pattern in the small intestine, and is characteristic of the fed state. Segmental contractions tend to occur over very short distances, typically less than 2 cm, and serve to mix the lumenal contents thoroughly. Short propulsive movements, on the other hand, provide the main mechanism by which the lumenal contents are moved down the intestine. These usually result in movement of the chyme over distances of 15 cm or less (41).

With the change in the ratio of segmenting to propulsive activity as a function of the phase of the motor pattern and upon meal ingestion, the efficiency of absorption also changes. Absorption is least efficient during Phase III (fasted state long range contractions), is intermediate during Phase I and Phase II and is greatest during the fed state motor pattern (42). Similarly, it is expected that because of better mixing, dissolution will also be most efficient in the fed state.

In the stomach and small intestine, movement of lumenal contents is virtually always in the distal direction. In the proximal colon, however, mixing can occur longitudinally as well as laterally, because some contractions drive the contents in the proximal rather than the distal direction. Figure 3 shows representative results from a study in which subjects ingested radio opaque markers with meals 36, 24, and 12 hours prior to radiography. Some of the markers taken 36 hours earlier are still in the ascending colon while some of the markers taken only 12 hours before are already at the end of the transverse colon (43). Based on these data, one may assume that some degree of mixing of fluids with solids occurs in the colon, although this has not been quantitatively defined.

Flow Rates in the GI Tract

Flow rates out of the stomach and at various locations in the small intestine have been measured in both the fasted and fed states. Emptying rates can be as high as 40 mL/minute immediately after ingestion of a 400 mL volume of normal saline (44). On the other hand, when small volumes are ingested in the quiescent phase of gastric motor activity the emptying rate may be virtually negligible (Table 9) (45). Nutrient fluids empty from the stomach according to zero order kinetics, with emptying dependent on caloric concentration. At a calorie density of 1 kcal/ml, about 2–2.5 mL/minute are emptied, whereas at 0.2 kcal/ml, about 10 mL/min are emptied (44).

Kerlin et al. (46) studied flow rates at various locations in the small intestine. They found that the flow of intestinal content is largely intermittent during fasting, with peaks of flow associated with passage of an activity front through the segment. Values stayed largely between 0 and 2 mL/min, with an average of 0.73 mL/min in the jejunum and 0.43 mL/min in the ileum.

Table 9. Lag Times and Time for Half of the Fluid to Empty, for 50 mL and 200 mL Saline Solutions Administered to Healthy Human Subjects

Volume administered	Phase I	Phase II	late Phase II/Phase III
50 mL			
lag time (min)	19	8	4
$t_{0.5}$ (min)	61	17	9
200 mL			
lag time (min)	16	5	2
$t_{0.5}$ (min)	23	12	5

Note: Excerpted from Ref. 45.

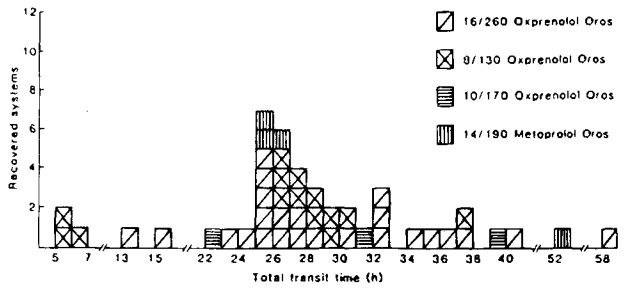

Fig. 4. Total transit time of osmotic pump dosage forms in healthy volunteers. (Reproduced with permission from Ref. 48).

After eating, flow rates increased to average of about 3 mL/min and 2 mL/min respectively, with values ranging from 0–7 mL/min.

Transit Data

Depending on where the drug is absorbed and how long it takes the dosage form to deliver the drug to these sites, the transit time used to calculate the appropriate duration of the dissolution test will differ.

Most drugs are not well absorbed from the stomach, which serves primarily a reservoir function. Because of its anatomical location and permeable mucosa, the small intestine is usually the main site of absorption within the GI tract. Owing to site specificity of transporters and exporters, as well as a tapering off in the unit surface area with distance down the small intestine, many substances are not equally permeable at all sites within the small intestine.

The proximal portion of the large intestine is, like the small intestine, derived embryonically from the midgut (41) and can thus serve as an absorbing organ for drugs. As of this writing, it appears that active transport mechanisms in this section of the gastrointestinal tract are limited primarily to electrolytes. Moreover, the tight junctions are considerably tighter than in the small intestine, restricting the passage of molecules via the paracellular route. Thus, the spectrum of drugs that can be efficiently transported is probably more restricted in the colon than in the small intestine. The distal part of the colon serves as a site for stool formation and storage, and for water conservation and is not generally regarded as being a viable site for drug absorption after oral administration.

Total Residence Time in the Gastrointestinal Tract

The total transit time imposes an overall limit on the duration of the release profile of the dosage form. Total transit time measurements were first reported by Hoelzel (47). He studied the passage of many types of materials, ranging in composition from gases to ball bearings. Total transit times ranged from two to six hours for gases up to 80 hours for high density objects. Materials with densities comparable to pharmaceutical products had transit time on the order of 1–3 days, consistent with the findings of a more recent study (48) (Figure 4) of the total transit times of osmotic pump dosage forms.

The total transit time is comprised of the residence times in the esophagus, stomach, small and large intestines, and rectum. In the absence of pathological conditions, esophageal residence time for most dosage forms is usually on the order of seconds to minutes (49), and thus plays a minor role in the overall transit profile. Gastric residence time is highly variable depending on motility patterns and food intake, whereas the small intestine residence time is relatively constant. In the large intestine, only the proximal residence time is likely to be relevant to drug delivery, since drug release and absorption from the transverse and distal segments is hindered by the paucity of available fluids, and by stool formation and storage.

Residence Times in the Stomach

Gastric residence time can be as short as a few minutes, or as long as half a day, depending on the fed/fasted status of the individual and the conformation of the dosage form. Fastest emptying of fluids occurs when they are taken without food, and in sufficient volumes. Emptying profiles of nonnutrient fluids administered at various phases of the fasted state motility cycle are presented in Table 9 (45).

In the *fasted state,* emptying of solids depends mostly on the phase of the motility cycle operative at the time of administration, and partly on the volume of fluid that is ingested along with the solid. If a small volume of water is ingested with the solid in Phase I (the quiescent phase of motility), first order emptying may not be induced, and consequently there may be a long lag time before either the water or the solid is emptied. For disintegrating solids, the ability of the particles to become suspended in the emptying fluid, along with the emptying pattern of the fluid, will be important to its emptying rate. For nondisintegrating solids greater than about 1 mm in diameter, emptying occurs mostly in late Phase II or Phase III (period of greatest activity) of the motility cycle. Since the average duration of the cycle is about 2 hours, average emptying time will be on the order of one hour, with a range of values between immediate emptying and a delay of two hours. The lack of size dependency in the emptying behavior for particles >1 mm is reflected by the gastric emptying times shown in Table 10 (50,51).

In the fed state, the motility cycle is replaced by a more regular contraction pattern in terms of both frequency and amplitude. Emptying of nutrient fluids is zero-order and calorie dependent, with about 2 kcal/minute emptied (44). Twelve ounces of soda pop contains about 140 kcal, so a ballpark estimate of emptying time in this case would be about 70 minutes. A specialized pattern of antral and pyloric contractions

Table 10. Emptying Times of Various Sized Dosage Forms in the Fasted State in Humans

Dosage form	Method	GRT[a]	Reference Number
25u microspheres	γ-scintigraphy	32–87 min	50
1 mm pellets	γ-scintigraphy	60–150 min	51
3 mm pellets	γ-scintigraphy	15–420 min	51
14 mm pellets	γ-scintigraphy	15–210 min	51

[a] GRT = Gastric residence time.

limits the size of the particles which are passed into the duodenum in the postprandial period to those smaller than about 1–2 mm in diameter (52). Ninety % of meal solids are emptied as particles less than 0.25 mm in diameter and almost none are greater than 2 mm. The distal stomach reduces the particle size of ingested solids to a fluid-like consistency. Undigested particles too big to stay suspended in this chyme are retained in the stomach until the reappearance of the fasted motor pattern (53).

Emptying times for nondigestible solids from the stomach in the fed state can vary widely because emptying depends on both the size of the solid particles and the meal that is coadministered. Representative results are shown in Table 11. Meyer et al. (52) calculated that the cutoff diameter for emptying in concert with the solid fraction of the meal is about 1.4 mm.

A second very important factor is the size of the meal. This is because meal emptying depends on the calorie content. Moore et al. (56) showed that the half-emptying times for meals containing 196 (fat: carbo:protein 18:15:67), 621 (6:14:80) and 1920 ± 206 (45:21:34) kcal. had half-emptying times of 77, 145 and 277 minutes respectively. Davis et al. (57) showed that the half-emptying time of 0.7 to 1.2 mm pellets was about twice as long when given with a heavy (900 kcal) as compared to a light (400 kcal) meal.

For a solid that is too large to empty with the meal, a delay of several hours prior to its delivery to the small intestine is likely, since in this case the food has to be cleared from the stomach before the fasted state motility cycle can be reestablished and the dosage form emptied under the auspices of Phase III activity.

Small Intestine Residence Time

In general, there is little difference in the mean transit times through the small intestine for liquids and solids, between the fed and fasted states, or for different types of dosage forms. Malagelada et al. (58) showed that the intestinal residence profiles for liquid and solids components of a meal are not significantly different, and that the transit time is on the order of one to three hours. Figure 5 summarizes the Nottingham data bank (59,60) for small intestinal residence times of various dosage forms in the fed and fasted states. As with the case of digestible materials, it seems that the small intestine has little capacity to differentiate between dosage forms with different sizes and densities, in sharp contrast to their residence behavior in the stomach.

Table 11. Representative Data for Emptying of Nondigestible Solids in the Fed State

Particle size	Method	GRT[a]	Reference Number
0.16-0.4 mm	γ-scintigraphy	34–75 min	54
1 mm	γ-scintigraphy	101 (±53)	52
1.6mm	γ-scintigraphy	152 (±69)	52
2.4mm	γ-scintigraphy	164 (±60)	52
3.2mm	γ-scintigraphy	152 (±40)	52
9 mm	x-ray	105 to >600	55
14 mm	γ-scintigraphy	180 to >780	51

[a] GRT = Gastric residence time.

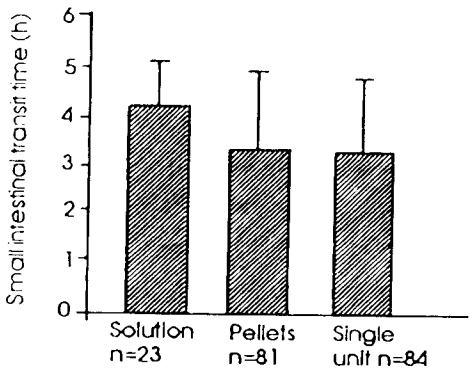

Fig. 5. Transit times of various dosage form types through the small intestine. Data for the fed and fasted state have been pooled. (Reproduced with permission from Ref. 59).

Residence Times in the Colon

Whereas the transit through the stomach and small intestine are on the order of minutes to hours, and each meal proceeds through without mixing with previous or subsequent meals, transit through the colon can be on the order of hours to days and there is extensive mixing of the contents (see Figure 3). Most of the mixing occurs in the proximal colon. Unlike the remainder of the GI tract, where the electrical waves that underlie the contraction patterns move almost exclusively in the *aborad* direction, in the proximal colon the direction is reversed, promoting delay of transit and facilitating the mixing required for the efficient absorption of water and electrolytes (41).

In the distal half of the colon, the final stages of fluid absorption occur, leading to the formation of feces for defecation. Therefore, the transit time of interest for calculating drug availability for absorption in the colon is the transit time across the proximal and transverse colon. In general, it seems that the size of the dosage form has little effect on the transit time, which is in any case quite variable. Values have been variously reported as 7 to 20 hours (60). Part of the variability appears to be attributable to the time of dosing, i.e. whether the dosage form is ingested in the morning or in the evening. Wilson et al. (61) have recently shown that there is little movement of single unit dosage forms in the colon during sleep.

COMMENTARY

Media Composition

Based on the physiological parameters presented in the previous Section, the following media can be suggested to

simulate gastric and small intestinal conditions in the fed and fasted state.

Gastric Media

Table 12 shows the composition of a test medium simulating gastric conditions in the fasted state. Gastric juice already in the stomach and secreted in response to fluid intake will result in an acid pH value in most volunteers. The sodium lauryl sulphate is present to reduce the surface tension to the reported values, since the components that lower the surface tension *in vivo* have not been unequivocally identified (62). Assuming that the coadministered fluid is water, the osmolality and buffer capacity of the medium will be low. Since secretions are at baseline values in the fasted state, the primary determinant of the volume will be the quantity of fluid that is ingested with the dosage form. In most bioavailability studies, 200–300 mL of water is given with the dose.

In the fed state, the lumenal composition in the stomach will be highly dependent on the composition of the meal ingested. A suitable starting point for design of a dissolution medium would be to homogenize the meal to be used in the clinical studies with the coadministered volume of water, and measure the pH, buffer capacity and osmolarity. A volume of oil reflecting the fat content of the meal can be added to an aqueous buffer simulating the afore-mentioned parameters, to produce an appropriate test medium. The use of long-life milk (63) and Ensure® (64) have been variously suggested as media suitable for simulating fed state in the stomach, in that they contain appropriate ratios of fat:protein:carbohydrate.

Intestinal Media

Key differences between gastric and intestinal conditions are the presence of bile and the higher pH value. Bile salts and lecithin facilitate the wetting of solids and the solubilization of lipophilic drugs (65) into mixed micelles. Thus, the dissolution of drugs may be enhanced considerably over the rate observed in plain aqueous solution. Sodium taurocholate was chosen as a representative bile salt because cholic acid is one of the most prevalent bile salts in human bile. Further, since the taurine conjugate has a very low pKa, there is little likelihood of precipitation or a change in the micellar size with minor variations in pH value. A suitable concentration of bile salt for simulating fasted state conditions would be between 3 and 5 mM (Table 13). Lecithin is present in an approximately 1:3 ratio with the bile salt, representative of the *in vivo* ratio which usually lies between 1:2 and 1:5.

Phosphate buffer is used as a substitute for the physiological buffer, bicarbonate, to avoid instability in the pH value due to reaction with oxygen. The pH value chosen is pH 6.8, which is generally representative of values measured from the mid-duodenum to the ileum (Table 3). Buffer capacity data (20) indicate that the buffer capacity in the fasted state is much lower than in the fed state or in the official dissolution medium, so the medium given in Table 13 is only lightly buffered. A volume of 500 mL would be consistent with the values reported in the literature for the volume in the fasted state.

Table 12. Dissolution Medium to Simulate Gastric Conditions in the Fasted State

HCl		0.01–0.05 N
Sodium Lauryl Sulfate		2.5 G
Sodium Chloride		2 G
Distilled Water	qs	1000 mL

Table 13. Medium Simulating Fasted State Conditions in the Small Intestine

KH_2PO4		0.029 M
NaOH	qs	pH 6.8
NaTaurocholate		5 mM
Lecithin		1.5 mM
KCl		0.22 M
distilled water	qs	1 L

pH = 6.8.
osmolarity 280–310 mOsm.
buffer capacity 10 ± 2 mEq/L/pH.

Many drugs that are very lipophilic (e.g. danazol, griseofulvin, BCS Class 2) are better absorbed when given with a meal than in the fasted state. Although changes in transit rate and increased volume in the fed state as well as specific food interactions may contribute to this increase, the increase in bile output could also be a key factor. The dissolution medium presented in Table 14 would be suitable for evaluating this effect. The medium contains acetate buffer instead of phosphate buffer, in order to achieve the higher buffer capacity and osmolarity while maintaining the lower pH value representative of fed state duodenal conditions. The taurocholate and lecithin are present in considerably higher concentrations than for the fasted state medium, and because of meal-induced secretions, a volume of up to 1 L would be reasonable.

After meal ingestion, fats and oils and their digestion products are also present, which may further modify the ability of some drugs to interact with the micelles (66). If the dosage form contains fatty excipients (e.g. some soft gelatin capsule formulations) and/or the drug is very lipophilic, it may therefore be worth considering the addition of mono- and diglycerides and lipase to the medium to simulate oily phase partitioning and digestion.

Duration of Dissolution Tests

The duration of the dissolution test must be tailored to not only the sites of absorption for the drug but also the timing of

Table 14. Medium Simulating Fed State Conditions in the Duodenum

Acetic acid		0.144 M
NaOH	qs	pH 5
NaTaurocholate		15 mM
Lecithin		4 mM
KCl		0.19 M
distilled water	qs	1L

pH = 5.
osmolarity 485–535 mOsm.
buffer capacity 76 ± 2 mEq/L/pH.

administration. If a drug is best absorbed from the upper small intestine and is to be administered in the fasted state, dissolution tests in a medium simulating fasted gastric conditions with a duration of 15 to 30 minutes are appropriate. On the other hand, if a drug is administered with food, and well absorbed throughout the small intestine and proximal large intestine, a duration of as long as 10 hours (with appropriate changes to the composition of the medium) could be envisaged.

Perhaps the most common case, though, is that of a drug that is reasonably well absorbed in the small intestine but less well absorbed in the colon, and which is given under fasted state conditions. In order to allow 1–2 hours for absorption in the small intestine, dissolution of such a compound would need to be completed under gastric conditions in 15 to 30 minutes and/or under proximal small intestinal conditions in one hour. In these circumstances, criteria of 85% dissolved after fifteen minutes in a gastric medium; after a combination of fifteen minutes in a gastric medium and fifteen minutes in a medium representative of conditions in the proximal small intestine; or after thirty minutes in a medium representative of conditions in the proximal small intestine would all be reasonable.

Hydrodynamic Model

Overall, most of the data available regarding hydrodynamics in the GI tract are qualitative in nature and not conducive to interpretation in terms of being able to select a representative flow pattern for dissolution test apparatus. The ability of the conventional dissolution testers to simulate hydrodynamics and flow patterns in the GI tract is open to question, since the studies that have been used to compare the testers with the *in vivo* conditions have consisted mainly of empirical *in vivo/in vitro* correlations. The recent work of Katori et al. (67), for example, indicated that for controlled release acetaminophen preparations, low agitation conditions correlated best with *in vivo* results. A lot more research in this area is sorely needed to establish suitable testing conditions for both immediate and controlled release products. In addition, the wide variety of mixing patterns found in the GI tract indicate that it is unlikely that a single setting (e.g. of flow rate or rotation speed) or apparatus can be used to simulate all motility conditions in the GI tract.

The flow-through tester is designed to simulate the flow patterns in the GI tract. Flow rates tend to be highest shortly after ingestion of a large volume of fluid into the stomach, and lowest during Phase I of motor activity in the stomach, and in the ileum. The flow rates suggested for application in the USP flow-through tester (1) are rather high (8 or 16 mL/min) compared to the physiological values, and unidirectional flow pattern is probably unrepresentative of the segmental mixing patterns in the small intestine and proximal colon. In the case of paddle and basket apparatus, the relationship between the hydrodynamics in the apparatus and those in the GI tract is even less clear. All-in-all, the simulation of the hydrodynamics in the GI tract is the remaining unknown in our quest to establish dissolution tests that are representative of the physiological conditions.

Summary

The parameters important to design of dissolution tests prognostic for *in vivo* dissolution behavior are the composition, volume and hydrodynamics of the dissolution medium and the duration of the test. Choice of dissolution test conditions should be based on where the drug is best absorbed in the gastrointestinal tract, and on whether it is to be dosed in the fed or fasted state. Although with our current knowledge of the physiology representative media can be selected to simulate gastric and intestinal conditions, and appropriate test durations can be chosen based on a knowledge of the drug's permeability profile in the gastrointestinal tract, the simulation of the in vivo hydrodynamics remains problematic and further research is needed in this area. Because of this deficiency, the dissolution test selected for a given product should be validated in terms of its ability to discriminate adequately between dosage forms that are not bioequivalent, as well as to exhibit similar release profiles for products that are bioequivalent.

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