A Proposed Food Breakdown Classification System to Predict Food Behavior during Gastric Digestion

Gail M. Bornhorst, Maria J. Ferrua, and R. Paul Singh

Abstract: The pharmaceutical industry has implemented the Biopharmaceutics Classification System (BCS), which is used to classify drug products based on their solubility and intestinal permeability. The BCS can help predict drug behavior *in vivo*, the rate-limiting mechanism of absorption, and the likelihood of an *in vitro–in vivo* correlation. Based on this analysis, we have proposed a Food Breakdown Classification System (FBCS) framework that can be used to classify solid foods according to their initial hardness and their rate of softening during physiological gastric conditions. The proposed FBCS will allow for prediction of food behavior during gastric digestion. The applicability of the FBCS framework in differentiating between dissimilar solid foods was demonstrated using four example foods: raw carrot, boiled potato, white rice, and brown rice. The initial hardness and rate of softening parameter (softening half time) were determined for these foods as well as their hypothesized FBCS class. In addition, we have provided future suggestions as to the methodological and analytical challenges that need to be overcome prior to widespread use and adoption of this classification system. The FBCS gives a framework that may be used to classify food products based on their material properties and their behavior during *in vitro* gastric digestion, and may also be used to predict *in vivo* food behavior. As consumer demand increases for functional and "pharma" food products, the food industry will need widespread testing of food products for their structural and functional performance during digestion.

Keywords: Food breakdown, rate of softening, gastric digestion, food classification system, food material properties

Introduction

Dissolution and absorption of drug products have been widely reported in pharmaceutical literature (Dahan and others 2009; Lindenberg and others 2004; Taupitz and others 2013; Radwan and others 2014; Radwan and others 2012; Courtney and others 2004). The Biopharmaceutics Classification System (BCS) was suggested by Amidon and others (1995) almost 20 years ago, and has since been adopted by the US Food and Drug Administration (FDA), the European Medicines Agency (EMEA), and the World Health Organization (WHO) to assist in developing bioavailability and bioequivalence standards for immediate-release oral drug products (Dahan and others 2009). The BCS groups drug products into four classes based on their solubility under physiological conditions and their intestinal permeability to predict the rate-limiting mechanism of absorption and the likelihood of an *in vitro–in vivo* correlation (IVIVC) (Amidon and others 1995).

Similar to the active ingredients in drug products, food materials also contain many "active ingredients." These active ingredients could be nutrients that are absorbed in naturally occurring foods, such as glucose from starchy-grains or amino acids from animal protein, or they could be substances added to a processed food material, such as calcium or iron-fortified breakfast products. Regardless of the active ingredient of interest, it is crucial to understand the behavior of the active ingredient as well as the matrix in which it is contained during the gastrointestinal (GI) digestion process. For food products, there is an additional step in nutrient absorption (as compared with drug absorption); the initial food structure must be mechanically and chemically broken down, allowing the nutrients to be released prior to their absorption. Additionally, food breakdown may influence drugs that are consumed with or after a meal because of the alterations in GI viscosity and/or rate of mixing (Weitschies and others 2005; Radwan and others 2012).

In recent years, there has been an increase in functional/specialty/"pharma" food products, with 6 out of the top 10 food trends for 2014 being related to food/nutritional functionality, and with 56% of consumers reporting that they purchased condition-specific pharma-food products in 2013 (Sloan 2014). These trends indicate an increasing need to understand the specific release and absorption of both naturally occurring food nutrients and added functional substances. This would allow for optimal design of foods with enhanced functionality.

The pharmaceutical industry has used the BCS as a tool to assist in drug product development, as it allows for prediction of drug behavior after consumption based on specific parameters that can be efficiently measured for each new drug. Because of the increase in consumer demand for functional and health-based food products, there is an imminent need to understand the mechanisms behind food breakdown, nutrient release, and nutrient absorption. Ideally, *in vivo* studies should be conducted to determine a food's behavior during digestion in the average consumer. However, because of resource and ethical considerations, extensive *in vivo* studies are rarely possible. Because of these constraints, if simple *in vitro* and/or initial food material properties can be correlated to food behavior *in vivo*, food product development and functional food optimization would be greatly enhanced.

These considerations have led us to propose a Food Breakdown Classification System (FBCS), grouping solid food materials into

MS 20142066 Submitted 12/17/2014, Accepted 2/24/2015. *Authors Gail M. Bornhorst and R. Paul Singh are with Dept. of Biological and Agricultural Engineering, Univ. of California, Davis, 1 Shields Avenue, Davis, CA 95616 U.S.A. Authors Maria J. Ferrua, and R. Paul Singh are with Riddet Inst., Massey Univ., Palmerston North, New Zealand. Direct inquiries to author Bornhorst (E-mail: gbornhorst@ucdavis.edu).*

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six classes that we have hypothesized will relate to their behavior after consumption. The classes are based on initial food hardness and a rate of softening parameter under simulated gastric conditions, two parameters that can be measured without extensive equipment or resources, allowing for widespread food classification. The objective of this classification system is to allow for prediction of food behavior during gastric digestion that can be completed by performing typical laboratory analyses. In the future, we hypothesize this information may be linked to other processes, such as gastric emptying, satiety, and rate of nutrient absorption. This framework will still require both *in vitro* and *in vivo* validation, however, this preliminary FBCS may be used to design and optimize future studies regarding food breakdown during digestion, creating a link between food material properties and their behavior after consumption.

Theoretical Considerations

A brief overview of the BCS

It is widely recognized that bioavailability of orally consumed drugs is primarily controlled by three factors: (1) dose, or amount of drug consumed; (2) dissolution, or the rate of dissolution of a drug under physiological gastric and intestinal conditions; and (3) absorption, or rate and permeability of the drug through the small intestinal wall. As such, dimensionless parameters have been developed that describe each of these controlling factors: the Dose number, Dissolution number, and Absorption number, respectively (Table 1). These dimensionless parameters have been determined for various drugs as a function of their properties and behavior *in vitro* and *in vivo* (Löbenberg and Amidon 2000; Amidon and others 1995). The Dose number, primarily governed by the dose of drug administered, can be modified by changing drug dosage, although the maximum dose may be limited because of toxicity concerns. The Dissolution and Absorption numbers are governed by drug properties, such as the concentration, particle size, and intestinal permeability and residence time (Table 1).

In the fundamental analysis presented by Amidon and others (1995), the intestine is modeled as a complex membrane–tube system, with the permeability of any drug product governed by Fick's First Law applied to a membrane. In this case, the interior of the membrane is the intestinal epithelium, with the intestinal contents as the influent content to the membrane, and the exterior of the membrane as the blood plasma. The blood plasma is regarded as a physiological sink (the concentration of any drug on the plasma-side of the membrane is assumed to be zero) because of the generally low concentrations of drugs in the plasma compared with the intestinal lumen. The absorption rate of a drug product (assuming no additional luminal reactions) can be described simply as the surface integral of the flux of drug through the membrane, which is the product of the effective drug permeability and the drug concentration (Amidon and others 1995).

A critical factor determining the flux of a drug across the membrane is its permeability. Permeability may be both position and time dependent, and these relationships can change for different drug products. Permeability may be position dependent because of the differing morphology in intestinal tissues from the duodenum to the colon. Time-dependent permeability may arise as a result of carrier-mediated transport of molecules across the intestinal epithelium. However, if the position and time dependence of the intestinal permeability are assumed to be similar for similar drug products, it can be implied that if two drug products have the same dissolution profile and the same permeability, they will be absorbed at the same rate and have the same bioavailability (Amidon and others 1995).

Drug concentration profiles along the intestine have been modeled assuming either complete radial mixing or as a well-mixed mixing tank. The drug concentration at any given position and time will be dependent on the *in vivo* dissolution rate, the initial dose (mass) of drug consumed, and the quantity of drug absorbed prior to the time of consideration. Predictions using a complete radial mixing pattern show good agreement with human absorption data (Sinko and others 1991). However, the specific hydrodynamics and mixing patterns in the intestine are described largely qualitatively, and merit an in-depth quantitative exploration, as they will play a large role in drug absorption (Dressman and others 1998).

The total mass of a drug product that is absorbed is a function of the absorption rate and the residence time in the small intestinal "tube." The profile of drug concentration across the intestinal tube can be modeled in several ways, depending on the type and amount of mixing that is hypothesized to occur. The intestinal residence time is calculated by using specified dimensions and material flow rates through the small intestine, assuming that the intestine is a cylindrical tube with a constant radius and length. Additionally, a constant flow rate is assumed, without accounting for any spatial or temporal variations in flow rate or mixing that may occur while the drugs are being absorbed (Amidon and others 1995).

The BCS was developed based on this initial theoretical framework, and groups drug products into one of four classes, based on their solubility and permeability (Table 2). From these classes, the rate limiting mechanism and the likelihood of an IVIVC are predicted (Amidon and others 1995).

Since the introduction of the BCS in 1995, it has become widely used in the pharmaceutical industry during the development and refinement of new and existing drug products. In particular, the BCS has been used to establish biowaivers for existing and new drug products. A biowaiver for a certain product allows for that product to be approved based on *in vitro* testing, such that it does not need to undergo rigorous *in vivo* testing in order to be approved. The link from the BCS Class and biowaiver consideration is because of the predicted IVIVC based on the BCS As BCS Class I drugs have the greatest likelihood of an IVIVC, regulators have allowed *in vitro* data to be used in place of *in vivo* data.

Currently, drugs assigned to Class I (high solubility and high permeability) can be considered for biowaivers, and recommendations have been made to allow biowaiver consideration for Class III drugs (high solubility, low permeability), if the products do not contain any permeability-modifying compounds in their formulation. Use of biowaivers has been especially important in the development of generic drug products, and in developing countries, where health budgets are limited and researchers and companies do not have the resources to conduct extensive *in vivo* trials (Dahan and others 2009).

Classification of widely consumed immediate-release drug products has been discussed in several reviews (Lindenberg and others 2004; Dahan and others 2009; Takagi and others 2006), and classes have been determined for 61 of the 130 WHO's Model list of Essential Medicines (Lindenberg and others 2004), as well as general classifications of the 200 most-widely consumed oral drug products in the United States, Great Britain, Spain, and Japan (Takagi and others 2006). Additionally, a provisional BCS service, with an online database allowing access to a variety of drug compounds with known classification data is offered by Therapeutics Systems Research Laboratories (Therapeutics Systems Research Laboratories 2014).

Table 1–Controlling factors and calculation of dimensionless parameters used in bioavailability analyses of drugs (Amidon and others 1995).

Dimensionless Parameter	Abbreviation	Calculation[a]	Controlling Factors
Dose Number	Do	$\frac{M_0/V_0}{C_s^{min}}$	- Amount of drug - Volume of gastric secretions - Drug solubility
Dissolution Number	Dn	$\frac{t_{res}}{t_{Diss}}$	- Drug diffusivity and concentration - Particle size and properties - Residence time in small intestines
Absorption Number	An	$\frac{t_{res}}{t_{Abs}}$	- Drug permeability in intestinal epithelium - Residence time in small intestines

[a] M_o, dose strength (mg); V_o, initial gastric volume (mL), approximately 250 mL; C_s^{min}, minimum solubility at physiological conditions (mg/mL); t_{res}, mean residence time in intestine, assuming constant flow rate and tube geometry (s), approximately 180 min; t_{Diss}, time required for a drug particle to dissolve (s); $1/t_{Abs}$, effective absorption rate constant through intestinal epithelium (1/s).

Table 2–BCS classes used to predict behavior of pharamaceutical products after ingestion and the likelihood of an *in vitro–in vivo* correlation (Emami 2006; Amidon and others 1995).

Class	Solubility (Dissolution Number)	Permeability (Absorption Number)	Rate Limiting Mechanism	*In Vitro–In Vivo* Correlation Expectation
I	High	High	Gastric emptying	Correlation expected if dissolution is slower than gastric emptying
II	Low	High	Dissolution	Correlation expected if similar in vitro and in vivo dissolution rates
III	High	Low	Absorption	Limited or no correlation expected
IV	Low	Low	Dissolution and absorption	Limited or no correlation expected

In addition to the BCS, a modified classification system, the Biopharmaceutics Drug Disposition Classification System (BDDCS) was proposed by Wu and Benet (2005), modifying the classification parameter of intestinal permeability to extensive or poor metabolism, designed to reflect the predominant route of drug elimination instead of solely the permeability through the intestinal epithelium. The BDDCS also allows for prediction of intestinal transporter effects on drug product behavior (Wu and Benet 2005).

Parallels to food digestion

Food breakdown and nutrient absorption may be described in a similar manner to drug dissolution and absorption. However, the food breakdown process is more complex, as there is both a structural, or physical, breakdown as well as a chemical breakdown that must occur prior to absorption. Similar to what has been described for drugs, the breakdown and absorption processes will be a function of the initial properties of the food, their behavior in the GI environment, the amount of time they spend in the given conditions (that is, residence time), and the physiological parameters of the GI environment. For example, specific drug or food properties that will influence dissolution/disintegration in the GI tract include particle size, molecular size, hydrophobicity, solubility, and crystal structure. Physiological parameters that will influence drug dissolution (or food breakdown) include pH, buffering capacity, amount of surfactants in gastric secretions and bile, GI viscosity, wall motility patterns, flow rate of contents, rate and amount of secretions, and other co-consumed fluids or foods in addition to the drug (or food) of interest (Dressman and others 1998).

Food physical, or macro-structural, breakdown through the GI tract will be influenced by initial food physical properties and their evolution when exposed to the physical and chemical conditions of the GI tract. Physical breakdown in the GI tract will primarily occur during mastication and gastric digestion. It will be influenced by the rate at which the matrix is softened by acid and enzymes, plus the extent and rate of overall breakdown. These processes will be controlled by the amount of time a food product is chewed, subjected to the acid/enzymatic gastric secretions, and how long it spends subjected to the antral contraction waves within the distal region of the stomach.

In addition to the physical breakdown and destruction of the food macro-structure, there must be a chemical breakdown of food materials into their constituent nutrient molecules. Chemical breakdown will occur as foods are subjected to the acidic and enzymatic environment of the GI tract. The rate and extent of chemical breakdown of foods will depend on their chemical composition and initial material structure. For instance, specific starch structure will play a major role in its rate of hydrolysis by amylase (Faulks and Bailey 1990; Butterworth and others 2011). Chemical breakdown will occur both during and after physical breakdown has occurred. For chemical breakdown to occur, the acid/enzymes must first have access to the food materials. The access of acid and enzymes to food materials will be a function of two processes, depending on the state of the food matrix. First, if the food structure is intact, the rate of diffusion of gastric secretions into the food matrix will control the rate at which gastric secretions will come in contact with the food material. Second, the rate of physical breakdown of the food matrix is crucial, as breakage of the food material will allow a greater surface area of food particles to come in contact with GI secretions while also releasing nutrient (that is, starch, protein, and lipid) molecules to be further broken down. Another factor that will be important in chemical breakdown of food nutrient molecules, regardless of their physical state, will be the residence time that the nutrient molecules are exposed to acid and enzymatic secretions. This residence time will be a function of the overall state of breakdown of the food and the mixing of gastric secretions with the ingested meal.

From this analysis, it can be observed that there are three main factors that play a role in physical and chemical food breakdown: (1) initial food properties (that is, structure, physical properties, and chemical composition), (2) rate of breakdown (that is, rate of softening and rate of hydrolysis), and (3) residence time in

physical or chemical environment necessary for breakdown (that is, time during mastication, time in antral region of stomach, and time exposed to acid or enzymes). The residence time (for either physical or chemical conditions) is interrelated to the rate of food breakdown and factors such as: quantity of secretions, location of secretions, mixing of contents, and gastric emptying rate, among other factors. Because of the complex nature of these relationships and the large number of unknown variables related to the residence time factor, it is difficult to make generalizations over a wide variety of situations. As such, the most logical factors to include in a food breakdown classification framework are the initial food properties and the rate of physical breakdown.

It should be noted that controlled-release drugs are not currently included in the BCS and are not considered for biowaviers in the same manner as immediate-release drugs. It may result that controlled-release drugs behave in the same manner as food products, since food physical structure essentially acts to control the release of nutrients into the GI tract. Previous studies have shown that extended release tablet absorption may be significantly influenced if they are taken with food because of the limited mixing in the stomach (Weitschies and others 2005). The development of a classification framework for food products may allow for parallels to be drawn with controlled-release drugs, further advancing their development. Additionally, as there is not a standard model to predict drug behavior when consumed with food (Custodio and others 2008), a food classification and characterization framework may allow for more in-depth study of the relationship between food and drug products that are consumed simultaneously.

Food Breakdown Classification System

Assumptions

Although food physical breakdown, chemical breakdown, and nutrient absorption are complex processes, it is necessary to make certain assumptions in order to construct an initial classification framework. Drug permeability (absorption) is a crucial factor in bioavailability and uptake of drugs, however, for this analysis, we will assume that the intestinal permeability of constituent nutrient molecules in foods (such as glucose, amino acids, and so on) will not be a controlling factor in their absorption. Additionally, we will not consider any inherent permeability differences between molecules that are absorbed via passive diffusion compared with carrier-mediated transport. Previous studies have shown that, for example, D-glucose and L-leucine both have a high permeability through the human jejunum and will be 100% absorbed, values much greater than for other drugs that have permeability-controlled absorption (Amidon and others 1995). Finally, we will not consider micelle formation, or any chemical breakdown of compounds that may occur because of the acidic and enzymatic conditions of the GI tract (such as breakdown of phytonutrients). However, these assumptions are areas for future study and refinement.

For this initial framework, we will focus on the processes of physical (macro-structural) breakdown of food. As only physical breakdown and not nutrient absorption is being considered here, we will focus on solid foods, excluding semi-solids and liquids that do not require significant physical breakdown during digestion. For this framework, solids are considered foods that have a definite shape and do not naturally conform to the shape of the container where they are placed. It should also be noted that matrices where a liquid phase is entrapped inside a three-dimensional colloidal or polymer network (that is, hydrogels) will also be considered as solid foods. We expect that, in food products, the breakdown of the food matrix will be a controlling factor to any nutrient hydrolysis and absorption. Since food breakdown is essentially the rate-limiting mechanism for release of nutrients from food matrices, we have chosen to focus on the physical/structural breakdown aspect of food products.

As a future step, we plan to add a secondary classification relating to the chemical aspect, with factors such as the initial chemical structure, rate of hydrolysis of nutrients (such as starches, proteins, and lipids), and intestinal permeability of digested molecules (such as glucose, monoglycerides, fatty acids, and amino acids) playing key roles in the bioaccessibility and bioavailability of specific nutrients.

Classification system framework

The proposed FBCS classifies food products based on: (1) their initial hardness, and (2) their rate of softening in physiological gastric conditions. These parameters were initially selected because they can be easily quantified with readily available laboratory equipment, such as a Texture Analyzer (Texture Technologies Corp., Scarsdale, N.Y., U.S.A.). The proposed FBCS identifies six classes of food products based on their initial hardness and rate of softening, along with the hypothesized rate-limiting breakdown mechanism and the expectation for an IVIVC (Table 3).

Food hardness can be measured by using a compression or penetration test. The hardness can be quantified as the peak, or maximum force (N) on the force–displacement curve during compression or penetration (Chen and others 2013; Bornhorst and others 2013c). Food initial hardness was selected as a classification parameter because it will influence the structural breakdown by means of the food resistance to fracture and erosion, as well as influencing the rate of acid diffusion into the matrix. It is hypothesized that the initial hardness parameter will be primarily influenced by the food moisture content and the extent of processing and/or cooking (Table 4).

Rate of softening was selected as the second classification parameter. It will be a limiting factor in the physical breakdown of most food products and can be easily measured *in vitro*. The rate of softening will be a function of the food structure and the amount of acid and enzymes that have entered the food matrix. For certain foods, the rate of softening will essentially be related to the dissolution of the food in gastric acid, similar to drug products (that is, hard candy, pretzels, see Table 5). The rate of softening may also be related to hydration of the food matrix, such as rehydration of dried food products and other food physical properties, such as porosity. For a majority of foods, the rate of softening will relate to the rate at which the matrix structure is weakened by acid and enzymes, which will be proportional to the rate of macro-structural breakdown that will occur in the gastric antrum as a result of the ACWs. For example, if a food, such as almonds, has a slow rate of softening, meaning that the gastric acid and enzymes do not easily penetrate the food matrix, or they have limited influence on the food structure, when subjected to the physical forces in the gastric antrum, the food will have a lower propensity to fracture and/or erode.

For illustration purposes only, food products that may fall within each of the proposed FBCS classes are given in Table 5. For example, Class I is hypothesized to contain a food product such as hard candy. Candy will have a high initial hardness, but when exposed to physiological gastric conditions, is hypothesized to essentially dissolve, leading to a fast rate of softening. Conversely, Class VI is predicted to contain fibrous structures, such as a piece of cooked meat. Cooked meat may not have a high initial hardness, because

Table 3–Proposed food breakdown classification system (FBCS) framework.

Class	Initial Hardness	Rate of Softening	Rate Limiting Mechanism	*In Vitro–In Vivo* Correlation Expectation
I	High	Fast	Dissolution rate and/or gastric emptying	Yes
II	Medium	Fast	Cellular disruption/breakdown	Yes, if cellular disruption achieved *in vitro*
III	Low	Fast	Dissolution & cellular disruption	Yes, if cellular disruption achieved *in vitro*
IV	High	Slow	Macro-structural breakdown & acid absorption	No
V	Medium	Slow	Macro-structural breakdown and dissolution	Yes, if dissolution rate is greater than macro-structural breakdown
VI	Low	Slow	Macro-structural breakdown	No

Table 4–Typical food product characteristics hypothesized for each of the six proposed classes.

		Rate of Softening	
		Fast	**Slow**
Initial hardness	**High**	(I)[a] Low moisture Dissolve easily in acid	(IV) Low moisture Compact structure
	Medium	(II) Intermediate moisture Cellular-tissue structure	(V) Intermediate moisture Compact structure
	Low	(III) High moisture Heavily cooked/processed	(VI) High moisture Fibrous structure

[a]Number in parenthesis shows the food breakdown class.

Table 5–Example foods that are hypothesized to fall within each of the six classes of the proposed food breakdown classification system.

		Rate of Softening	
		Fast	**Slow**
Initial hardness	**High**	(I)[a] candy, pretzel, uncooked vegetables	(IV) seeds/nuts (almond, peanut)
	Medium	(II) apple, cheese, white rice	(V) cooked pasta, brown rice
	Low	(III) soft fruit (peach, pear), cooked vegetables	(VI) cooked meat

[a]Number in parenthesis show the food breakdown class.

of its moisture content, but is anticipated to have a slow rate of softening, because of the fibrous structure.

Rationale for selection of classification parameters

The proposed FBCS classifies food products based on their initial hardness and their rate of softening in physiological gastric conditions. The rationale for selection of these parameters was based on an analysis of previous studies that examined food texture before and after simulated gastric digestion along with food particle disintegration during simulated gastric digestion. An example of this data is given in Table 6. These data are only given as an example and is not meant to represent all digestion studies conducted up to this point.

The selected data show the relationship between initial hardness, rate of softening, and rate of disintegration. In general, the initial hardness and the rate of softening have a similar relationship to the rate of disintegration, such that a lower initial hardness and lower rate of softening relate to faster disintegration, although this may not always be the case. If two products with similar initial hardness are compared, it can be observed that not only initial hardness, but also rate of softening appear to play a role in the disintegration behavior of the food material (Table 6). For example, ham (initial hardness of 4.1 N) and carrots boiled for 6 min (initial hardness of 5.3 N) have similar initial hardness, but carrots have a greater estimated rate of softening compared with ham (58×10^{-3} N/min compared with 0 N/min, for carrots and ham, respectively). The faster estimated rate of softening for carrots follows the same trend as the rate of disintegration, as the 6 min boiled carrots had a faster rate of disintegration compared with ham (80×10^{-3} compared with 68×10^{-3} L/min, for carrots and ham, respectively). These data suggest that *both* the initial hardness and the rate of softening of a food material are important parameters needed to predict food disintegration behavior during gastric digestion.

This example data has shown the relationship between the disintegration parameter (rate of disintegration) and the classification parameters (initial hardness and estimated rate of softening), which has been used as the rationale that these classification parameters will have a relationship with food disintegration and breakdown during gastric digestion. Additionally, this previous study has shown that both an initial hardness and a rate of softening classification parameter may be necessary to adequately classify food breakdown during gastric digestion.

Limitations

The FBCS proposed here was developed through careful consideration of previous work in the pharmaceutical area and previous

Table 6–Relationship between disintegration and classification parameters for previously published data on ham and carrots (Kong and Singh 2008).

		Disintegration Parameter[a]	Classification Parameters	
Reference	Food Material[b]	Rate of Disintegration (1/min) x 10^3	Initial Hardness (N)	Estimated Rate of Softening (N/min) x 10^3 [c]
Kong and Singh (2008)	Ham[d]	68	4.1	0
	Carrot: 6 min boiled[d]	80	5.3	58
	Carrot: 2 min boiled[d]	67	17.0	258
	Carrot: Raw[d]	52	42.3	360

[a]Disintegration, as defined in this study, was the mass lost by food particles when subjected to certain hydrodynamic and mechanical forces in a simulated gastric fluid at 37°C.
[b]All food products were in the shape of 6 mm diameter cylinders.
[c]Although texture kinetics were not measured in these studies, the estimated rate of softening was calculated using the initial hardness and the hardness after a certain time period of static soaking in simulated gastric fluid, assuming zero order kinetics. Since only two data points were available, zero order kinetics were assumed to allow for estimation of a rate of softening.
[d]For these materials, the rate of disintegration was calculated as the parameter k from the equation $\gamma = 1 - \left(1 - e^{-kt}\right)^{\beta}$, and the hardness was determined by calculation of the maximum force during a compression test with a 40 mm cylinder (Kong and Singh 2008).

food digestion studies. However, the FBCS has been presented here as a hypothesis that merits future study to refine the classification parameters and the associated outcomes for each class. At this point, the rate-limiting mechanism for breakdown and the probability of an IVIVC (Table 3) have been hypothesized based on the BCS (Amidon and others 1995). Future studies regarding both of the rate-limiting breakdown mechanisms and the expectation for an IVIVC for foods from each class may be undertaken in order to provide sufficient evidence to support these classification system outcomes.

An additional limitation to the FBCS is the absence of standard classification methods. The preliminary analyses and proposed methods presented here are based on the combined expertise of the authors in this area. However, standard methods need to be developed in terms of the sample preparation (including the presence of an oral processing step), *in vitro* digestion method, measurement methodology, and kinetic parameter analysis. A detailed discussion of some of these limitations and suggestions for future studies is given in section *Measurement Methodology and Example Classification*.

Another limitation of the proposed FBCS is that the analysis presented here only considers consumption of a single food product, and does not take into account the differences in breakdown when multiple foods are co-consumed as part of a mixed meal. The interactions between different food products of varying physical properties may be a topic of future study to determine if the FBCS class changes for certain foods if they are co-consumed with other food products.

Measurement Methodology and Example Classification

Example calculation of classification parameters

Based on the FBCS framework described in section *Food Breakdown Classification System (FBCS)*, we hypothesized that food initial hardness and rate of softening from texture kinetic data could be calculated, and these values would vary for different food products. To explore this hypothesis, we selected previously gathered sets of data that included both initial hardness and texture kinetics (that is, texture changes at multiple time periods during *in vitro* or *in vivo* gastric digestion). The initial hardness was quantified as the maximum force during compression of either individual food particles or during bulk compression of a certain sample volume. The texture changes were fit to the Weibull model:

$$\frac{H_t}{H_0} = e^{-(kt)\beta} \quad (1)$$

where H_t is the hardness (N) at time t, H_0 is the initial hardness (N), k is the scale parameter, which may indicate the rate of change in hardness (L/min); t is the digestion time (min); and β is the distribution shape factor (dimensionless). The Weibull model has been extensively used in pharmaceutical research to model the dissolution profile of solid dosages (Costa and Sousa Lobo 2001) and provided the best fit (R^2) to the example texture data used in this analysis.

A softening half time ($t_{1/2}$) was calculated as the time necessary for the initial hardness to be reduced by 50% using the following expression:

$$t_{1/2} = \frac{1}{k}\left(\ln(2)\right)^{1/\beta} \quad (2)$$

where $t_{1/2}$ is the time necessary for the initial hardness to be reduced by 50%, and k and β are the Weibull model parameters described above and determined in Eq. (1). The softening half time was used to describe the rate of softening in this preliminary analysis. The softening half time incorporates both the k and β parameters from the Weibull model, and will more appropriately describe the overall curve properties than either one of the fitted parameters on its own. Because of the challenges in describing the rate of softening of the food matrices, determination of specific rate of softening parameters is an area for future study.

From the example classification data presented in Table 7, the measurement method, property considered, and digestion method varied for each type of food; however, it was still possible to classify the food product behavior, which follows with our hypothesis that the selected classification parameters can be used to classify different food products. The initial hardness varied from 8 (boiled potato) to 278 N (raw carrot). The softening half time varied from 7 (raw carrot) to 79 min (brown rice). Results highlight the need for the two classification parameters (that is, initial hardness and rate of softening) to categorize food products. For example, two products with similar initial hardness, such as brown and white rice (85 compared with 79 N, respectively) have quite different softening half time values (brown rice $t_{1/2} = 79$ min compared with white rice $t_{1/2} = 21$ min). Similarly, foods with comparable softening half times may not necessarily have a similar initial hardness. For example, boiled potato and raw carrot (static soaking method) had softening half times of 10 and 12 min, respectively. However, boiled potatoes had an initial hardness of 8 N compared with 278 N for raw carrots.

To allow for the optimal comparison between different products, experimental method and analysis techniques must be refined and kept constant across foods. For example, raw carrots were tested

Table 7–Classification parameters (softening half time and initial hardness) for selected test foods calculated from previously collected data.

Measurement Method	Property	Digestion Method[a]	Food Type	Initial Hardness (N)	Softening Half Time $t_{1/2}$ (min)[b]	Hypothesized FBCS Class[c]	Reference
Bulk Compression[d]	Hardness	Hydrodynamic Chamber	Raw Carrot	278	7	I	Unpublished data
	Hardness	Static soaking	Raw Carrot	278	12	I	Unpublished data
Individual Compression[e]	Failure strength	Static soaking	Boiled Potato	8	10	III	Drechsler and others (2014)
	Hardness	*In vivo* digestion	White Rice[f]	79	21	II	Bornhorst and others (2013c)
	Hardness	*In vivo* digestion	Brown Rice[f]	85	79	V	Bornhorst and others (2013c)

[a]Specific parameters for each digestion method can be found in the reference for each table entry; both hydrodynamic chamber and static soaking are examples of *in vitro* digestion methods.
[b]$t_{1/2}$ is calculated as the time in minutes that is required for the food texture to become 50% of its initial value Eq. (2).
[c]The hypothesized FBCS class was determined based on the class parameters described in Table 7.
[d]Bulk compression tests were conducted as described in Bornhorst and others (2013a).
[e]Individual compression tests were conducted as described in Bornhorst and others (2013c).
[f]Values were taken from the proximal stomach region, as described in Bornhorst and others (2013c).

both during static soaking and also using a hydrodynamic digestion chamber (Kong and Singh 2008). During static soaking, the carrots had a softening half time of 12 min. However, during soaking in the hydrodynamic digestion chamber, their softening half time was only 7 min. Differences in digestion and analysis method may result in variations in the rate of softening classification parameter. As such, the hypothesized FBCS classes are subject to future refinement after additional experiments can be conducted under controlled conditions (*in vitro* digestion method, experimental, and analysis), which is ongoing work in our groups.

Based on the data presented in Table 7, hypothesized ranges for the initial hardness and rate of softening classification parameters are given in Table 8. The values presented in Table 8 are hypothesized based on our preliminary analysis of existing data and were used in the classification of the foods given in Table 7. For the development of a more refined set of classification parameters, it will be necessary to complete a series of experiments employing consistent experimental methodology, using foods with varying hardness and structure.

FBCS class versus *in vivo* breakdown behavior

To further support our hypothesis that the proposed classification system can be adequately used to classify food products into categories that will relate to their breakdown behavior during *in vivo* digestion, we have compared the FBCS class of rice (brown and white) to its *in vivo* performance during gastric digestion.

Table 9 shows a comparison of digestion and classification parameters for brown and white rice. In this case, all of the measurements used for parameter calculation (both digestion and classification parameters) were taken from the same *in vivo* study conducted using the growing pig as a model for an adult human (Bornhorst and others 2013c; Bornhorst and others 2013b). The digestion parameters considered were the breakdown rate and the gastric emptying rate. The breakdown rate was determined by examining changes over time of the gastric digesta rheological properties, as digesta rheological properties have been previously shown to be a good indicator of the overall state of meal breakdown (Guerin and others 2001). The gastric emptying rate was determined by fitting gastric emptying curves to a modified power-exponential model (Bornhorst and others 2013b). Gastric emptying was also used as a parameter for comparison because for food materials to empty from the stomach, they must have reached a certain amount of breakdown, and the rate of gastric emptying is indicative of the overall rate of breakdown of a meal.

This analysis showed that the breakdown rate can be inversely related to the softening half time. For example, white rice in the distal region had the greatest rate of breakdown (23.7×10^{-3} L/min) and the shortest softening half time (7 min), indicating that it both broke down and softened faster compared with the other experimental conditions.

Differences in the rate of gastric emptying between brown and white rice were also reflected in the classification parameters. For example, white rice experienced a faster gastric emptying and a faster rate of breakdown compared with brown rice (4.1 compared with 3.4 L/min gastric emptying rate). The differences between classification parameters for brown and white rice also follow a similar trend. Regardless of the stomach region, white rice had a shorter softening half time compared with brown rice. Comparing between only samples from the distal region, white rice had a softening half time of 7 min compared with 21 min for brown rice.

It is interesting to note that white and brown rice had similar initial hardness (79 compared with 85 N) values, but different rates of softening and breakdown *in vivo.* This example case demonstrates the necessity of both of the selected classification parameters in differentiating food behavior (gastric emptying and breakdown rate) *in vivo*.

Measurement methodology

The data presented in Table 7 were collected using different measurement methods under a variety of different experimental conditions. To standardize the FBCS, the same measurement method and experimental conditions should be used for all studies.

Possible measurement methods for initial hardness and rate of softening are presented in Table 10. The methods presented in Table 10 to evaluate the food initial are based on our experiences from previous studies, and need to be compared in terms of their sensitivity to measure the quantities of interest across different food products, their ease of use, and the amount of sample required, in order to develop a single method for use with a wide variety of food products. When measuring the initial hardness, other food mechanical properties, such as failure strength, cohesiveness, modulus of elasticity, toughness, and work to compress may also be considered.

Table 8–Hypothesized ranges for the classification parameters of initial hardness and rate of softening.

Parameter	Category	Hypothesized Range
Initial hardness[a]	High	Hardness > 100 N
	Medium	20 > Hardness > 100 N
	Low	Hardness < 20 N
Softening half-time $t_{1/2}$[b]	Fast	$t_{1/2}$ < 30 min
	Slow	$t_{1/2}$ > 30 min

[a]Ranges for initial hardness were developed assuming that hardness was measured using individual particle compression or bulk compression methods as described above.
[b]These values were developed assuming calculation of the rate of softening parameters as described in Table 7.

Table 9–Comparison of classification parameters with *in vivo* digestion behavior for brown and white rice from *in vivo* studies completed in growing pigs as previously described (Bornhorst and others 2013c; Bornhorst and others 2013b; Bornhorst 2012).

Food Properties		Digestion Parameters		Classification Parameters	
Rice Type	Stomach Location[a]	Breakdown Rate: $\beta \times 10^3$ (1/min)[b]	GE Rate: $k \times 10^3$ (1/min)[c]	Initial Hardness (N)	Softening Half-time $t_{1/2}$ (min)[d]
White	Distal	23.7	4.1	79	7
White	Proximal	16.2			21
Brown	Distal	2.3	3.4	85	21
Brown	Proximal	3.5			79

GE, gastric emptying.
[a]Proximal and distal refer to the sampling region within the stomach, where proximal is the upper region of the stomach, and distal is the lower region of the stomach, as described in Bornhorst and others (2013c).
[b]Breakdown rate was calculated as the parameter β from the equation $y = (1 + k\beta t)\, e^{-\beta t}$, which was fit to the changes in rheological flow behavior of gastric digesta samples over a 480 min digestion period as described in Bornhorst (2012).
[c]Gastric emptying rate was calculated as the parameter k from the equation $y = 1 - \left(1 - e^{-kt}\right)^{\beta}$ as described in Bornhorst and others (2013b).
[d]Softening half time was determined as described in Table 7.

Table 10–Advantages and disadvantages of selected measurement methods for the proposed FBCS system classification parameters.

Parameter	Measurement Method	Advantages	Disadvantages
Initial Hardness	Individual particle penetration	- Determination of extent of softening (i.e. soft/tender layer)	- High variation between individual particles
	Individual particle compression	- Commonly used analysis (similar to texture profile analysis) - Less variability than penetration test	- High variation between individual particles
	Bulk compression	- May provide more consistent results - Results represent the overall material structure that may give better correlation to overall breakdown - May be useful for non-uniform samples	- Does not examine specific softening of each particle - Requires larger amount of sample
Simulated gastric conditions	Static or agitated soaking in water bath	- Easy to conduct tests; no need for specialized equipment	- No hydrodynamic or physical forces on particles
	Immersion in hydrodynamic chamber	- More accurate representation of hydrodynamic forces	- Need for specialized annular cell/hydrodynamic chamber
	Use of dynamic mechanical model	- More accurate disintegration profile accounting for physical forces	- May not be possible to analyze individual particle softening due to particle breakage - Requires dynamic model and advanced operator knowledge

During *in vivo* food digestion, prior to softening and breakdown in the stomach, foods are subjected to oral processing, which involves a breakdown and mixing process with saliva. Inevitably, the particle size after mastication will influence food breakdown and rate of softening because of an increase of contact surface area for gastric acid and enzymes. Accordingly, the particle size after chewing and the prior extent of softening from α-amylase will influence the rate of softening in gastric conditions. However, large variations in food particle size after chewing occur because of both individual and food factors including food composition, food hardness, and dental status of the subject. Data from several studies have shown a non-linear relationship between food hardness and the mean particle size of foods after mastication (Chen and others 2013). The variations in particle size and chewing behavior result in a significant challenge to design comparable experiments across varying food types that are representative of a typical adult human. The influence of particle size on rate of softening is a variable that merits additional exploration in the follow up experiments for this proposed classification system. It is recommended that food products be cut into uniform cubes of sizes between 1 and 10 mm to represent the particle size breakdown during oral processing. The size of food particles after mastication varies and follows a distribution, with median particle sizes varying from less than 1 mm to greater than 3 mm in different natural food products (Jalabert-Malbos and others 2007). Although using cubes of a uniform size may not completely represent the bolus of masticated food that enters the stomach, it will allow for determination of the influence of particle size on rate of softening. Additionally, standardization of

the food particle size will facilitate repeatability between samples and comparison of results. If particle size reduction during oral processing results in significant modifications to the FBCS, it may be considered as an additional classification parameter in the future.

In addition to the method used to evaluate the initial hardness and rate of softening, the experimental setup used for the simulated gastric digestion will also be a critical factor in determining the FBCS parameters. As illustrated in Table 7, the immersion of carrots in the a hydrodynamic chamber instead of static soaking resulted in a softening half time 58% higher compared with the softening half time during static soaking (7 compared with 12 min, respectively), indicating that the hydrodynamic chamber resulted in faster particulate softening. As such, various alternative systems are given (Table 10).

In addition to the measurement method, other experimental factors that need to be considered during the *in vitro* digestion studies to determine the rate of softening are: particle size (single size compared with size distribution), simulated saliva addition (if added, quantity and α-amylase concentration), gastric fluid composition (enzymes, pH), temperature and variations in homeostatic mechanisms, and amount of time to conduct the test (short enough intervals to capture all changes taking place, long enough total time to capture majority of softening process and adequately describe kinetics).

The selection of an ideal measurement method for the classification parameters (initial hardness and softening half time $t_{1/2}$-) will require a detailed comparison of the different methods for similar food products, and is an area that merits future study. Additionally the model selected for data analysis, and the analysis parameters used for classification must be selected to adequately represent the kinetic behavior of the food particles during the digestion process. For the proposed FBCS framework, the follow-up step will be to determine a standard methodology that will allow for data to be collected over a wide range of products, but still be comparable between different foods.

In Vitro–In Vivo Correlation

To assist in product development of functional pharmaceutical or food products, a correlation must be drawn between the ability of *in vitro* testing to predict the *in vivo* response of any given product under analysis. In the previous section, we illustrated that the proposed classification parameters determined during *in vitro* testing may reflect the *in vivo* disintegration of food particles. However, to be able to use *in vitro* testing to predict *in vivo* behavior, an IVIVC must first be established, especially if *in vitro* testing will be used to influence regulatory decisions. We will present here a discussion of the methods of establishing an IVIVC in the pharmaceutical industry as well as examples of *in vitro–in vivo* comparisons that have been previously made with food products. In the pharmaceutical industry, the BCS is a fundamental tool that can be used during drug development to predict whether it will be possible to develop an IVIVC with a certain drug product (Emami 2006). As such, we have included this discussion to show the potential for future linkages between our proposed FBCS and regulatory actions for food products.

The US Food and Drug Administration (FDA) released a guidance document in 1997 to the pharmaceutical industry on the possible levels of IVIVCs as well as how to develop IVIVCs, and their applicability to product development and regulatory approvals (Food and Drug Administration Center for Drug Evaluation and Research 1997). The IVIVC may not be the same for all products; five levels of IVIVC have been established. The IVIVC level is assigned based on the type of correlation found between *in vitro* and *in vivo* data, and have important implications in the procedures for product development and any potential regulatory actions (Table 11).

There are many variations in methodological and analytical techniques used to develop an IVIVC. To illustrate the general procedure, we will describe the protocol laid out in the FDA guidelines for developing a Level A IVIVC. The first step in development is to determine the *in vitro* dissolution profiles (apparatus and fluid may vary) of ideally, at least three different formulations of the same active ingredient. These different formulations should represent a slow, medium, and fast *in vitro* dissolution profile. In addition to the *in vitro* dissolution testing, *in vivo* absorption tests in humans must be conducted. The *in vivo* plasma drug concentration profiles for the different formulations can be used to determine a predicted *in vivo* drug dissolution profile using numerical deconvolution or other numerical techniques. The resulting *in vivo* drug dissolution profile can then be compared with the *in vitro* dissolution profile for the various drug formulations. The trends observed *in vitro* and *in vivo* should be the same to ensure a correlation. For example, if there is a 25% difference between the slow and fast dissolving drug formulations *in vitro*, there should be a 25% difference between the *in vivo* dissolution profiles of the slow and fast dissolving drugs. The IVIVC should be consistent across formulations (that is, slow, medium, and fast dissolving drugs should have the same type of correlation). If a scaling factor is used to match the *in vitro* and *in vivo* dissolution profiles, this factor must be the same for all formulations. Furthermore, the *in vitro* dissolution testing parameters must adequately discriminate between different formulations, and should not be changed for different formulations once appropriate parameters have been developed (Food and Drug Administration Center for Drug Evaluation and Research 1997).

Once an IVIVC is established for a particular drug formulation(s), it may be used for process control and quality assurance, determination of release characteristics over time, and facilitation of regulatory approval after minor changes have been made. Regulatory approval for minor changes, such as change of manufacturing site, change of drug strength, or change of non-active ingredients in the formulation may be approved if a biowaiver is given. A biowaiver will be given if adequate data exist to suggest that the new product demonstrates the same behavior as the previous product *in vitro*. A biowaiver may be given for a Level A or multiple-level C correlation and would allow for minor changes to be made to the product without the necessity for additional *in vivo* studies to show bioequivalence (same dissolution and absorption behavior). This facilitates regulatory approval of product changes without the use of human studies, allowing *in vitro* testing to serve as a surrogate for *in vivo* studies in the cases where a biowaiver is approved.

Similar regulatory approval is not necessary at the present time in the food industry for functional food products. However, as the demand for science-based claims on food labels and advertising increases, it will be crucial to develop *in vitro* methods that can predict the *in vivo* behavior of functional food products. There have been previous studies that have correlated some type of *in vitro* parameter to an *in vivo* response after consumption of different food products. We will discuss a few of these correlations, although this is not meant to represent a comprehensive review of IVIVCs in the literature. This discussion is aimed to give various examples of previous *in vitro* studies that have successfully correlated *in vitro* parameters to *in vivo* responses after food consumption. This may demonstrate the potential for further development of IVIVCs in

Table 11–Summary of *in vitro–in vivo* correlation (IVIVC) levels and their applications in product development and regulation (Emami 2006; Food and Drug Administration Center for Drug Evaluation and Research 1997).

Level of *In Vitro–In Vivo* Correlation	Values or Parameters Compared for Correlation	Applications of Correlation
A	Point-to-point relationship of *in vitro* and *in vivo* dissolution curves or of *in vitro* dissolution curve to *in vivo* absorption curve; generally linear relationship between curves, can be made with or without scaling factor	Highest level of correlation and can be used to apply for biowaiver; *in vitro* data can be used to predict profiles *in vivo*
B	*In vivo* mean dissolution or residence time compared with *in vitro* mean dissolution time using statistical moment analysis	Only limited predictability[a]; not useful for regulatory purposes
C	One *in vitro* dissolution time point (median, 90th percentile, and so on) to one *in vivo* pharmacokinetic parameter (area under the absorption curve, maximum plasma/serum concentration, and so on)	Useful information for initial product development and formulation, but limited predictability[a]
Multiple Level C	Multiple parameters from level C; correlation must be made at least three different time points (beginning, middle, and end of dissolution profile)	High level of predictive capability, indicates Level A correlation is also likely; can be used in product development and to apply for biowaiver
D[b]	Rank order of products *in vitro* and *in vivo*	Useful for initial product development, but because of lack of quantitative information; not useful for regulatory approval

[a]Limited predictability because of the fact that multiple dissolution profiles could yield the same mean dissolution or residence time; a single parameter cannot effectively distinguish between products with different dissolution and absorption profiles.
[b]Level D correlation not officially recognized by the FDA, but described by Emami (2006).

the food industry, using similar methods to those described above in the pharmaceutical industry.

The digestion and absorption of carbohydrate-based food products have been widely studied in food and nutritional research because of their implications on metabolic conditions, such as diabetes. *In vitro* digestibility has been investigated using a wide range of experimental conditions/setups (including different sample preparations, enzymes, solutions, and time points tested). *In vivo* response is usually measured based on the blood glucose response (the glucose concentration in the blood at certain intervals after the meal) and the glycemic index (area under the blood glucose response curve) (Jenkins and others 1981). It has been shown that there was a 95% correlation between the rate of hydrolysis *in vitro* (percent starch hydrolyzed/30 min) to the peak glucose response *in vivo* (μmol glucose/mL above fasting level) (O' Dea and others 1981) for intact and ground brown and white rice meals. Similarly, Goñi and others (1997) correlated a "hydrolysis index," or the percent of starch hydrolyzed after 90 min *in vitro* with the glycemic index (measured *in vivo*) for a variety of carbohydrate-based foods common in the Mediterranean diet, such as bread, pasta, rice, and lentils.

Other quantities that have been correlated between *in vitro* and *in vivo* studies of carbohydrate-based food products include the resistant starch and rapidly available glucose. Englyst and others (1996) compared the resistant starch content in wheat, potato, and banana biscuits determined using an *in vitro* method with the starch content recovered from ileostomy patients. Since ileostomy patients have a collection bag at the end of the ileum (small intestine), they allow for an *in vivo* testing method to determine the amount of a certain nutrient digested in the upper GI tract. In this study, they found a good correlation between the *in vitro* and *in vivo* measurements of resistant starch, where resistant starch was defined as the amount of starch and starch-degradation products that are not digested and absorbed in the small intestine. In another study, Englyst and others (1999), found that the rapidly available glucose in several foods, including pearled barley, spaghetti, corn flakes, and white bread, determined by an *in vitro* digestion method was correlated to the *in vivo* glycemic index.

In addition to carbohydrate-based food products, a dual *in vitro–in vivo* digestibility assay (*in vitro* + *in vivo* animal model) has been correlated to *in vivo* organic matter absorption in humans (Coles and others 2013). Instead of using a solely *in vitro* digestibility approach, Coles and others (2013) used an *in vivo* rat model to describe digestion up to the small intestine of diets containing differing amounts and sources of dietary fiber, coupled with an *in vitro* model of large intestinal fermentation. The organic matter digestibility *in vitro* was correlated to the *in vivo* fecal digestibility of organic matter (for the same diets) from human subjects. Although this model uses *in vitro*, human, and animal models for its correlation, it may present new opportunities to develop IVIVCs for food energy and nutrient availability.

Although all of these models have been shown to exhibit an IVIVC with various types of food products, the correlation was only based on a single data point, which would represent either a Level B or Level C correlation, according to the pharmaceutical standards (Table 11). In the future, to develop a more robust correlation between *in vitro* digestion studies and *in vivo* food behavior, it may be useful to take a similar approach to that laid out by the FDA for the pharmaceutical industry. The development of strong IVIVCs for functional food products will assist in their product development, and in the future, may even facilitate approval of health claims.

Conclusions and Future Considerations

We have proposed here a FBCS that may be used to predict the *in vivo* behavior of a wide variety of solid food products. In the future, standard methods for *in vitro* digestion assays (that is, time, pH, enzymes, and so on) as well as the texture measurements will need to be finalized. Additionally, the kinetic analysis of texture data is an area that merits an in depth exploration to determine the most appropriate parameter that can be used to describe texture kinetics during the digestion process, yet can differentiate between foods with different behavior. For this analysis, we have chosen the softening half time to represent the texture kinetics, which appropriately differentiates between the behavior of the selected food products. However, with a larger data set of controlled experiments, the analysis of the texture kinetics may need modification.

Once these standard experimental and analytical methods have been developed, we expect that a large variety of food products

of varying structure and composition will be tested to determine their predicted FBCS class. Following this, products with different *in vivo* behavior will be compared with determine if the FBCS class adequately corresponds to their behavior *in vivo*. Although we have demonstrated here that the FBCS classification for white and brown rice is functional to differentiate between their varying behaviors *in vivo*, these comparisons will need to be made for a larger selection of food products.

In addition to method development and widespread testing, other aspects of the food digestion and absorption process may be incorporated into the FBCS. These aspects include the chemical breakdown of nutrients, as well as intestinal absorption, permeability, and transport. Furthermore, additional methods may be developed to include liquid and semi-solid foods to the FBCS as well as food mixtures (for example, various foods that may be consumed together as part of a typical mixed meal).

In summary, we have presented here the framework for a FBCS that may be used to predict the *in vivo* behavior of solid food products during gastric digestion using easily measurable parameters, such as food initial hardness and softening half time. We have hypothesized certain food products that will fall into each category along with their characteristics. We expect that the proposed FBCS can be used as a powerful tool in future food development and optimization, as it will allow for prediction of a food product's *in vivo* breakdown based on *in vitro* laboratory tests.

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