Structuring food to control its disintegration in the gastrointestinal tract and optimize nutrient bioavailability

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Didier Dupont[a*], Steven Le Feunteun[b], Sébastien Marze[c], Isabelle Souchon[b]

[a] STLO, Agrocampus Ouest, INRA, 35000, Rennes, France

[b] UMR GMPA, AgroParisTech, INRA, Université Paris-Saclay, 78850, Thiverval-Grignon, France

[c] UR BIA, INRA, 44000 Nantes, France

* Corresponding author:

Dr Didier Dupont

Science and Technology of Milk and Eggs (STLO)

INRA Agrocampus Ouest

65 rue de Saint-Brieuc

35000 Rennes, France

Tel: +33223485335

Fax: +33223485350

e-mail: didier.dupont@inra.fr

Dr Steven Le Feunteun

Food Process Engineering and Microbiology

AgroParis Tech INRA

Avenue Lucien Brétignières

78850 Thiverval-Grignon, France

E-mail: steven.le-feunteun@inra.fr

Dr Sébastien Marze

Biopolymers, Interactions, Assemblies

Rue de la Géraudière

44316 Nantes Cedex 3, France

E-mail: sebastien.marze@inra.fr

Dr Isabelle Souchon

Food Process Engineering and Microbiology

AgroParis Tech INRA

Avenue Lucien Brétignières

78850 Thiverval-Grignon, France

E-mail: isabelle.souchon@inra.fr

Abstract

Unravelling the fate of food in the gastrointestinal tract is essential to better understand the health effects of food and fight against diet-related pathologies such as cardiovascular diseases and type-2 diabetes, and enable the design of food of high nutritional and sensory qualities to provide humans with a healthy diet. Research to date has mostly considered foods according to their composition. However, the role of the food matrix, i.e. the microstructure-level organization of nutrients and their interactions, in the digestive process was recently demonstrated. This paper summarizes the work done by different groups at the INRA to understand and model food digestion. Integration of the knowledge acquired will serve the development of a reverse engineering approach to design new foods purpose- adapted to meeting the nutritional needs of specific populations like infants or the elderly.

Keywords

Food matrix – digestion – health – modeling – reverse engineering – nutrient bioavailability

Introduction

The past few decades have seen a dramatic increase in diet-related pathologies worldwide. Obesity and its consequences on the increased prevalence of pathologies such as cardiovascular disease and type-2 diabetes affect around 1.5 billion adults in the world today, and most predictions tend to show that the number will reach 3 billion people by the 2030 horizon (WHO, 2013). Worldwide, the proportion of adults with a body-mass index (BMI) of 25 kg/m² or greater increased between 1980 and 2013 from 28.8% to 36.9% in men and from 29.8% to 38.0% in women (Ng, et al., 2014). This rise in obesity prevalence is observed within all age categories, including the elderly, and appears to be higher for women (15.1%) than men (13.9%). The number of people who die every year from obesity has been estimated at 2.8 million. In France, according to the last national epidemiological study, 6.9 million people are considered obese, and the percentage of obese people has climbed from 8.5% in 1997 to 15% in 2012 (Roche, 2012). The increase in obesity is mainly due to (1) consumption of high-calorie foods and (2) a lack of physical activity due to sedentary work patterns, increasing use of mechanized transport, and urbanization. Despite many public information campaigns, it remains difficult to get overweight people to increase their physical activity. The only solution is therefore to offer consumers a wide variety of foods that are less caloric but have similar nutritional, satiation, satiety and sensory properties.

The digestive process, or how to transform food into nutrients available for humans

Food disintegration during digestion results in the release of nutrients that will be available to maintain homeostasis. The oral phase is crucial, especially for solid and semi-solid foods. Mastication, the first mechanical step of digestion, transforms food into smaller particles ready to be lubricated. Saliva aggregates masticated food into a bolus before swallowing, and protects the soft mucosal surface from damage by coarse foods. It also acts as a solvent of flavor compounds and contains enzymatic activities that initiate macronutrient digestion, particularly hydrolysis of carbohydrates. Salivary α-amylase can hydrolyze a large proportion of starch before food reaches the small intestine (Bornhorst & Singh, 2012) depending on the food buffering capacity able to maintain gastric pH within a range where this enzyme is still active and on the dramatic loss of structural organization of starch granules (gelatinization) in response to heat treatment. The oral phase also allows the release of molecules responsible for the flavor that can act as biological signals and generate satiety. When food enters the stomach, the bolus will encounter a dramatically different set of physical–chemical conditions to the oral cavity. Acid secretions produced by the gastric mucosa and digestive enzymes such as gastric lipase or pepsin will transform the bolus into a chyme, dramatically affect food structure, and modulate

gastric emptying rate. Gastric emptying rate depends on the caloric charge of the meal and the osmolarity and structures of the chyme. Macronutrient hydrolysis, initiated in the stomach for proteins and lipids and in the mouth for carbohydrates, will be completed in the small intestine under the action of highly efficient enzymes such as pancreatic lipase, trypsin, chymotrypsin, elastase and pancreatic α-amylase. This is also where most nutrient absorption will take place, due to the structure of the intestinal epithelium which is covered with villi that increase the absorption surface. The intestinal epithelium also releases myriad enzymes that help complete the breakdown of nutrients before their absorption (Babusiak, Man, Petrak, & Vyoral, 2007). The epithelium is also covered by a mucus layer whose protective effect against pathogenic bacteria stems from the presence of glycoproteins, i.e. the mucins, but also DNA granules generated by epithelial cell apoptosis. Bile salts facilitate the ability of a food particle to pass this protective layer (Macierzanka, Mackie, Bajka, Rigby, Nau, & Dupont, 2014). Finally, undigested constituents, in particular both soluble (pectin, alginate, carrageenans, etc.) and insoluble (cellulose, hemicellulose, lignin) dietary fiber, will reach the large intestine where they will be metabolized by the intestinal microbiota. The whole digestive process is regulated by gastrointestinal hormones that can slow down or accelerate gut motility. For instance, an excess of triglycerides reaching the ileum (distal part of the small intestine) will end up in the production of GLP1 and PYY peptides that will slow down gastric emptying, allowing better hydrolysis and absorption of lipids. Sensors are visibly found along the entire gastrointestinal tract (and especially in the duodenum) where they are able to bind dietary peptides, free fatty acids and micronutrients to regulate the digestive process (Akiba & Kaunitz, 2014). The importance of nutrient homeostasis for human health is manifest, yet little is known about direct nutrient-sensing mechanisms. This is currently a hot research topic, and lipid, amino acid and glucose sensing mechanisms and signaling events were recently reviewed (Efeyan, Comb, & Sabatini, 2015).

Why do we need to understand the mechanisms of food disintegration in the gastrointestinal tract?

The digestive process has been extensively studied and the events occurring in the gut are relatively well-known, even if nutrient sensing and brain-gut axis connections need further exploration (Efeyan, et al., 2015; Gonzalez-Arancibia, et al., 2016). However, for food itself, less is known about the structural modifications that occur within the gastrointestinal tract. Most studies to date have been limited to either monitoring nutrients in the bloodstream or demonstrating the physiological effects of a diet, with no real understanding of the food disintegration mechanisms involved. A better understanding of the mechanisms underpinning digestion is likely to improve our knowledge on the

kinetics of macronutrient hydrolysis and bioaccessibility and, consequently, nutrient bioavailability. This insight should enable the whole digestive process to be mathematically modeled. The main outcome of this kind of mathematical model would be the ability to develop a reverse engineering approach (**Figure 1**) consisting in starting from the biological or nutritional effect we want to obtain and deducing the most appropriate food structure, and consequently the most relevant processing conditions, to obtain it.

Does the food matrix structure play a key role in food digestion?

Until recently, it was considered that the structure of the food matrix had a limited impact on food digestion and that the only parameter affecting digestion was food composition in terms of proteins, lipids and carbohydrates. However, in the past few years, new evidences have clearly demonstrated that food matrix structure plays a key role in the kinetics of macronutrient transit and hydrolysis (Parada & Aguilera, 2007; Turgeon & Rioux, 2011). Among the most striking examples, the impact of cooking carrot on carotene bioavailability has been investigated in several *in vivo* studies (Livny, et al., 2003; Tydeman, et al., 2010). At identical composition, carotene release in the gastrointestinal tract is linked to the disintegration of cellular structures, and carotenoid bioaccessibility has been shown to be inversely correlated to carotenoid bioencapsulation. From a processing standpoint, thermal or mechanical processing of fruit- and vegetable-based food products prior to consumption is essential to open up the structural organization in which the carotenoids are embedded and thus enhance their release from the food matrices (Lemmens, Colle, Van Buggenhout, Palmero, Van Loey, & Hendrickx, 2014). Another example is the impact of the lipid droplet size of an emulsion on lipid digestion and absorption. Changing the homogenization conditions made it possible to modulate mean lipid droplet size (0.7/10 µm). Consequently, 20–37% of triglycerides were hydrolyzed in the stomach with a 0.7 µm droplet size *vs.* 7–16% with a 10 µm droplet size (Armand, et al., 1999). Substantial differences were also found in the duodenum, with 57–73% of triglycerides hydrolyzed for the fine emulsion compared to only 37–46% for the coarse one. When the same triglycerides were given to humans in emulsified *vs.* non-emulsified form as part of a standardized breakfast, the kinetics of postprandial plasma triglycerides was faster and higher for the emulsified form, especially in obese subjects (Vors, et al., 2013). Food structure also has a well-known influence on carbohydrate digestion. For instance, the glycemic index (GI) of a bread depends on its density (d) (Saulnier, et al., 2010). A basic French baguette (d=0.16) presented a GI of 75 whereas another one with identical composition but higher density (d=0.24) presented a GI of 55, due to its lower starch accessibility. Indeed, GI is not considered a characteristic of the human being but rather a property of the food item itself (ISO, 2010). Similarly,

the influence of food structure at various scales of pasta on the digestion of starch and proteins has been extensively studied (M. Petitot, Abecassis, & Micard, 2009). The structure of cooked pasta is generally described as a compact matrix with starch (a polymeric carbohydrate composed of amylose and amylopectin) granules entrapped in a protein network. When heated in excess water, starch granules absorb water and swell. This phenomenon, named gelatinization is caused by the disruption of the native crystalline structure of starch granules. As granules continue to expand, amylose is released from the intergranular phase to the aqueous phase. Cooling the gelatinized starch/water mixture to room temperature induces the re-crystallization of starch molecules (mainly amylose); this process is known as retrogradation. During digestion, the rate of starch hydrolysis in pasta is related to various parameters. Among those, the degree of gelatinization and retrogradation of starch granule and the amylose-to-amylopectin ratio seem to play a key role (Akerberg, Liljeberg, & Bjorck, 1998). Pasta size (i.e. vermicelli *vs*. spaghetti) and shape (i.e. macaroni *vs*. spaghetti), which depend on the forming step, seem also to be major factors, likely due to differences in surface-to-weight ratio leading to differences in accessibility of amylase to starch (Granfeldt, Bjorck, & Hagander, 1991; Wolever, et al., 1986). High pasta drying temperatures were shown to decrease the *in vitro* digestibility of starch in cooked pasta (Maud Petitot, Brossard, Barron, Larré, Morel, & Micard, 2009). The hypothesis to explain this phenomenon was high drying temperatures driving high levels of intermolecular protein cross-linking, leading to more intense starch encapsulation, decreasing its susceptibility to enzymes. Higher drying temperatures were also shown to decrease protein digestibility *in vitro* (Stuknyte, et al., 2014). The higher resistance of proteins to digestion could be attributed to the presence of highly aggregated proteins stabilized by covalent protein interactions, such as inter-peptide cross-linking and Maillard-type aggregates (De Zorzi, Curioni, Simonato, Giannattasio, & Pasini, 2007).

Finally, studies have been conducted to demonstrate the effect of processing on the mechanisms of nut digestion. A first set of experiments compared the *in vivo* kinetics of digestion of raw *vs*. roasted almonds using the pig as a model, and showed that roasting decreased protein gastric emptying and tocopherol bioavailability (Bornhorst, Roman, Rutherfurd, Burri, Moughan, & Singh, 2013). Proteolysis was more intense in raw almonds, and some spatial differences were also observed with a higher degree of proteolysis in the distal section of the stomach (Bornhorst, Drechsler, Montoya, Rutherfurd, Moughan, & Singh, 2016). A study comparing the effects of boiling, roasting and frying peanuts found that processing improved gastric disintegration of peanut particles by modifying their water absorption and ultimately improving their softening (Kong, Oztop, Singh, & McCarthy, 2013)

These examples clearly show how processing modifies kinetics of macronutrient digestion. However, structure differences in these examples occur mainly at molecular or supramolecular level (changes in protein structure, aggregation, etc.), and there are fewer examples of comparisons between foods

with different macrostructures. In this context, the only way to really demonstrate the effect of food structure on hydrolysis in the gastrointestinal tract is to compare the behavior of food of identical composition and caloric charge but different macrostructure. To illustrate, six liquid, gelified or semi-solid dairy matrices (skim raw or heat-treated milks, stirred and unstirred acid gel, raw or heat-treated rennet gel) manufactured from the same milk powder (**Figure 2**) were given to six mini-pigs fitted with two cannulas in the duodenum and mid-jejunum and equipped with a catheter in the abdominal aorta. Gastric emptying half-time was shown to be directly influenced by food structure, at 98 min for the liquid matrices increasing to 148 min for the acid gel (Le Feunteun, et al., 2014). Gel stirring led to an intermediate viscous liquid structure and, consequently, to an intermediate gastric emptying half-time of 124 min. Rennet coagulation significantly increased gastric emptying half-time. It was shown that rennet gel was transformed into a dense curd in gastric conditions and that the curd was slowly eroded by pepsin in the stomach, thus explaining the longer retention of the matrix in the stomach and the dramatic increase in gastric emptying half-time (Barbe, Menard, et al., 2014). This definitively demonstrates that at identical composition and caloric charge, food matrix structure regulates gastric emptying. These data were obtained on pigs that are considered as the best model for mimicking the upper part (i.e. stomach and small intestine) of the human tract (Kararli, 1995; Roura, et al., 2016). Indeed, very similar trends were also observed in one of the only studies done on humans, where liquid milk was found to empty more rapidly than yogurt (i.e. acid gel), thus modifying the kinetics of proteolysis (Gaudichon, et al., 1995)

Quantification of milk proteins in the duodenal effluents showed significant between-sample differences in kinetics of proteolysis in the small intestine (**Figure 3**). After ingestion of milk, caseins and whey proteins massively and rapidly entered the duodenum, but after 30 mins their concentrations quickly fell back down to basal levels. In contrast, acid gel led to a lower but much longer-lasting increase of milk proteins than liquid milk (Barbe, et al., 2013). Similarly to gastric emptying, stirred gel exhibited an intermediate behavior between milk and non-stirred acid gel. Finally, rennet gel led to low concentrations of milk proteins throughout digestion with a slight increase after 7h of digestion, thus confirming the slow erosion by pepsin of the curd formed in the stomach (Barbe, Menard, et al., 2014).

Quantification of plasma amino acids showed similar patterns to those observed for milk proteins in the duodenum. For leucine (**Figure 4**), like the other amino acids, milk led to a sharp and early peak whereas dairy gels led to a lower and later peak. Again, stirred gel showed an intermediate behavior between milk and non-stirred gel, and rennet gel led to very low amino acid levels in the bloodstream. Quantification of plasma ghrelin (**Figure 5**) showed a strong decrease in the hormone's concentration

in the hours following an acid gel ingestion compared to milk ingestion, indicating that acid gel consumption could favor satiety.

Digestion of milk proteins is accompanied by the release of a myriad of peptides in the gut lumen. The identification of these peptides showed that the pattern is also highly influenced by food structure. In particular, the kinetics of appearance and disappearance of the peptides known to exert biological activity (antimicrobial, immunomodulatory, anti-hypertensive, etc.) were shown to be different for the six dairy matrices studied (Barbe, Le Feunteun, et al., 2014).

For lipids, we have used various structural approaches to control bioaccessibility. First, we tried to modulate the interfacial layer of emulsion droplets. Indeed, type of emulsifier was previously reported to influence lipid digestion *in vitro*, with lipid emulsifiers slowing digestion down compared to protein emulsifiers (Mun, Decker, & McClements, 2007). We thus compared various processes of intestinal digestion of triglyceride droplets (individual or in emulsion) stabilized by either a lipid emulsifier (sodium oleate) or a protein emulsifier (β-lactoglobulin). Despite significant differences in the initial mechanical properties of the interfacial layer, only minor effects emerged (Marze, 2015; Marze & Choimet, 2012; Marze, Choimet, & Foucat, 2012). This was attributed to the adsorption of bile salts desorbing most other molecules (except lipases) from the interface, thus lowering the mechanical properties to the same values in both cases (Marze & Choimet, 2012). We also measured some structural characteristics (including interfacial layer thickness) *in situ* using synchrotron small-angle X-ray scattering, which showed that they were not significantly affected by emulsifier type throughout intestinal digestion (Marze, Gaillard, & Roblin, 2015).

Another strategy to modulate the bioaccessibility of nutrients or micronutrients is to create a specific bulk encapsulation structure. We tested a w/o/w double emulsion as a delivery system for betanin (a hydrophilic betalain from red beet) during *in vitro* intestinal digestion (Kaimainen, Marze, Jarvenpaa, Anton, & Huopalahti, 2015). In the digestion medium with no pancreatic lipase and no bile salt, the double emulsion structures remained stable, so there was no betanin release from the inner water droplets. In contrast, in the presence of pancreatic lipase and bile salt, betanin was released gradually due to aggregation of w/o/w globules and coalescence of w/o inner water droplets as oil lipolysis proceeded.

Other parameters (see the mathematical modeling section) and structures (McClements & Li, 2010) should be tested to assess the potential of various emulsions as delivery systems in the context of nutrition and satiety research (e.g. by accelerating lipid transit in order to trigger the ileal brake). One of the next challenges is the digestion of more complex foods, where different types of nutrients are released concurrently, possibly with synergistic or competitive interplays. For instance, proteolysis

kinetics strongly impacts the lipolysis kinetics of oil-in-water emulsions entrapped in a protein network, whereas these reactions seem mainly independent when the same emulsion is dispersed in a liquid protein solution (Mat, Le Feunteun, Michon, & Souchon, 2016). However, such variations in the continuous emulsion phase may also influence gastric emptying kinetics, as evidenced for dairy products, and/or possible lipid layering in the stomach. Unravelling the various effects of food structure properties on digestion thus remains a challenging—but promising—area of research.

Mathematical modeling of digestion; can we predict the physiological effect of food?

The complexity involved in modeling the digestive process makes it an extremely ambitious goal. Food digestion in the upper part of the gastrointestinal tract co-opts several mechanical (chewing in the oral cavity, grinding and mixing in the stomach, etc.) and enzymatic (hydrolysis by digestive enzymes) processes. Digestion can therefore be seen as a cascade of biological events that can be translated into mathematical equations. Some human gastrointestinal tract models have been developed, making it possible to integrate knowledge available on gut physiology and relationships between the different organs involved (Liao, Zhao, & Gregersen, 2009). Some approaches have focused on one specific compartment of the gastrointestinal tract. Computational modeling of the dynamics of gastric digestion and fluid dynamics in the human stomach, for example, has focalized an intense and innovative research effort (M. J. Ferrua & Singh, 2010; Maria J. Ferrua & Singh, 2011; M. J. Ferrua & Singh, 2015). The data obtained underlines the complex interaction of food material properties and physiological parameters that control the behavior of different digesta systems during gastric digestion. Powerful retropulsive jet-like motions caused by the stomach contractions in the pylorus area play a key role in suspending, breaking and dispersing gastric contents during digestion (Schulze, 2015)

Most of the *in silico* models available are compartmental models that take each independent section of the gastrointestinal tract into consideration as well as the flows between them, and describe both by a series of differential equations (Rivest, Bernier, & Pomar, 2000; Strathe, Danfaer, & Chwalibog, 2008; Wilson & Dainty, 1999). However, most of these models have never been validated against *in vivo* data, and none of them take the structure and physical properties of food into account.

Our team recently developed a model of milk protein digestion and absorption using data collected during the *in vivo* trial on mini-pigs with the 6 dairy matrices previously described in **Figure 2** (Le Feunteun, et al., 2014). Data used to build the model were the duodenal concentrations of milk proteins (**Figure 3**) and plasma amino acids (**Figure 4**). The model was purpose-constructed not only to represent the main physiological events but also to account for several phenomena presumably

occurring within the stomach. We tested different behavioral hypotheses for each matrix, and only selected the best model structures. A further originality of our model is that it accounts for the main fluxes arising in the digestion process, thus enabling insight into quantities that were unobserved during the original experiments, such as endogenous secretions, stomach volume or gastric emptying kinetics. However, even though the model enabled progress in understanding the digestive process, it is far from being predictive; for instance, it is impossible at this stage to predict the pattern of peptide release in the gut lumen according to dairy product structure.

Some structural aspects of emulsified triglyceride digestion (namely bioaccessibility, the first step towards bioavailability) were also modelled, using two approaches. One approach was based on multi-agent simulation, reproducing the digestion processes at single triglyceride droplet scale (Marze, 2014, 2015). As this type of simulation relies on spatiotemporal and contact rules for different particles (agents), it serves to test a host of situations. We were thus able to simulate the bioaccessibility kinetics of lipophilic vitamins in a triglyceride droplet and investigate various parameters (structural, compositional, digestive). We showed that lipophilic vitamin bioaccessibility is controlled by triglyceride digestion, which is mainly influenced by triglyceride type, vitamin form (free vs. esterified), and digestion conditions (*in vitro vs. in vivo*). Other parameters such as droplet size and gastric lipolysis had less significant effects. Switching from increasing proportions of triglycerides to a non-digestible oil (limonene) led to decreasing vitamin A bioaccessibility at a given digestion time, or to increasing digestion times before reaching a given vitamin A bioaccessibility.

The other approach was based on mass transfer differential equations, serving to quantify the role of most physical–chemical parameters (Marze & Choimet, 2012). The most important parameters were initial droplet interfacial area and volume fraction, molar mass of the emulsified triglyceride, and the mechanical properties of the interfacial layer. Zeroth-order and first-order kinetics equations were derived. The most studied so far is the zeroth-order kinetics initially derived by Li & McClements (Li & McClements, 2010) with an error, further corrected by Gaucel et al. (Gaucel, Trelea, & Le Feunteun, 2015). Both kinetics orders were found to suitably describe droplet digestion processes, but only a few papers have evaluated their predictability according to their parameters. **Figure 6** illustrates the fitting of two independent measurements of intestinal digestion of emulsified triglyceride by a first-order kinetics equation, which was found to better represent the data than a zeroth-order one. In both cases, the mass transfer coefficient was the only fitted parameter (Marze & Choimet, 2012).

We also developed a model of lipid hydrolysis that quantitatively reproduced the remarkable effect the coalescence of oil droplets coalescence on their *in vitro* hydrolysis kinetics (Giang, et al., 2015). This model has been further improved to predict kinetics of incorporation of all their constitutive fatty

acids within the bile salt micelles (**Figure 7**) (Giang, et al., 2016). Thanks to these promising results, we are currently modeling the fate of fatty acids *in vivo*, from their ingestion through to their release into blood plasma, using a dataset similar to the one obtained for proteins in mini-pigs. Our idea is to keep a common basis with the model of protein digestion and absorption (secretions, transit, etc.) ready to combine both models in the future. Long-term perspectives of this modeling strategy are to predict more complex kinetics of food digestion by considering the postprandial fate of the different classes of nutrients contained in a food or even a meal.

Performing clinical trials on animals and humans is getting increasingly difficult for ethical and economic reasons. In turn, *in vitro* digestion models remain relatively limited for reproducing physiological reality, which makes the challenge now to design *in silico* models to predict the fate of food in the gastrointestinal tract.

Reverse engineering: integrating our knowledge on food digestion to design new foods perfectly adapted to human nutritional needs

As described above, our knowledge of the precise mechanisms of food digestion has significantly improved in the past few years. In particular, we now a sharper picture of the way food structure affects transit time in the different digestive compartments and the kinetics of macronutrient hydrolysis. However, the physiological consequences of these differences of hydrolysis kinetics are still unknown, and research is needed to determine whether the changes in kinetics of macronutrient hydrolysis and nutrient bioavailability have an impact on human health. We do know that fast protein hydrolysis allowing rapid release of branched-chain amino acids into the bloodstream can serve to restore muscle protein synthesis in elderly people suffering from sarcopenia, i.e. aging-related muscle loss (Rieu, et al., 2007). But are the benefits similar for other target populations, e.g. neonates or healthy adults, or in pathologic cases? What about the other macronutrients (lipids, carbohydrates)?

The physiological consequences of a modification of residence time in the stomach are partly known. For instance, it has been reported that slower gastric emptying tends to generate satiation and/or satiety. It is therefore possible to develop a reverse engineering strategy in order to integrate this knowledge and design foods whose structure will increase their residence time in the stomach. Since dairy proteins are known to enhance satiety, two yogurts containing high levels of milk proteins (8 g of protein/100 g yogurt instead of 3 g protein/100 g yogurt for a conventional product) were designed. Both yogurts had exactly the same composition, but one had a high viscosity whereas the other had a low viscosity. The gastric emptying half time of these 2 yogurts was estimated in pigs by gamma-scintigraphy and compared to that of an iso-caloric yogurt enriched with starch. Yogurts were labeled

with technicium-99 and given to 12 conventional pigs (35 kg), and gastric emptying was followed by gamma-scintigraphy during the first 3h after yogurt ingestion.

The results obtained (**Figure 8**) showed that gastric emptying was slowed down for the yogurts enriched with milk proteins. Only the difference between the low-viscosity yogurt and the starch-enriched control yogurt was statistically significant ($p<0.05$), whereas the difference observed between the high-viscosity yogurt and the control yogurt was not significant, likely due to higher variability in the data obtained with the high-viscosity yogurt. The next step is to determine whether these differences in gastric emptying time observed in pigs will generate satiety in humans.

A structural approach could also be used for lipids to let fatty acids reach the ileum (ileal brake), which is known to slow down the whole GI transit process, inducing both satiation and satiety (Maljaars, Peters, Mela, & Masclee, 2008). This could be achieved using delivery systems that initially accelerate lipid transit and/or prolong their kinetics of release and, thus, their kinetics of absorption.

The transit time of a food in the gastrointestinal tract modulates the kinetics of its metabolism by the body. Designing foods with controlled transit time would therefore allow better control of the kinetics of nutrient availability and thus better fit the nutritional needs of specific populations. This will probably be one of the key near-future challenges for the food industry to integrate these concepts and move towards a more “personalized nutrition” for humans.

Conclusion

The past 10 years have seen a multidisciplinary scientific community composed of nutritionists, gut physiologists and food scientists make significant progress to show that the fate of food in the gastrointestinal tract depends, among other things, on the structure of the food matrix. Food cannot be considered simply as an addition of proteins, lipids and carbohydrates. The way these constituents are organized and interact with each other within the matrix affects the fate of food in the gastrointestinal tract. It is therefore of paramount importance to integrate this new knowledge in order to design food that is better adapted to the nutritional needs of specific populations, such as infants, the elderly, and the overweight. Key to achieving this goal is to design food that is structured to undergo modifications in the stomach that will make them more or less prone to disintegration, and therefore modulate the kinetics of macronutrient hydrolysis and nutrient bioavailability. A joint effort between academia and industry is required in order to reach this goal.

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572 **Figure captions**

573

574 **Figure 1**. Understanding the fate of food in the gastrointestinal tract to design new foods by reverse
575 engineering.

576 **Figure 2**. Design of six iso-caloric dairy matrices of identical composition but different microstructure.

577 **Figure 3**. Evolution of β-lactoglobulin (left) and casein (right) concentrations as measured in the
578 duodenum of 6 mini-pigs fed a heated milk, acid gel, stirred acid gel and rennet gel of identical gross
579 composition.

580 **Figure 4**. Evolution of leucine concentration in plasma of mini-pigs fed a heated milk, acid gel, stirred
581 acid gel and rennet gel of identical gross composition.

582 **Figure 5**. Evolution of ghrelin concentration in plasma of mini-pigs fed a heated milk, acid gel, stirred
583 acid gel and rennet gel of identical gross composition.

584 **Figure 6**. Fatty acid release during *in vitro* intestinal digestion monitored by pH-stat (dotted line),
585 modeled by first-order kinetics including a solubility parameter (full line). Mass transfer coefficient and
586 bioaccessibility are fitted. Emulsions of triolein stabilized by β-lactoglobulin (pink) or sodium oleate
587 (green) or emulsions of tricaprylin stabilized by β-lactoglobulin (red) or sodium oleate (black).

588 **Figure 7**. Comparison between modeled and experimental time-course of the bioaccessibility of
589 individual lipolysis products (i.e. contained within the bile salt micellar phase) during *in vitro* intestinal
590 digestion. Symbols are means ± sd over 3 replicated digestion experiments, and solid lines represent
591 the model simulations.

592 **Figure 8**. Gastric emptying of yogurts enriched in low-viscosity and high-viscosity proteins and an iso-
593 caloric placebo

594

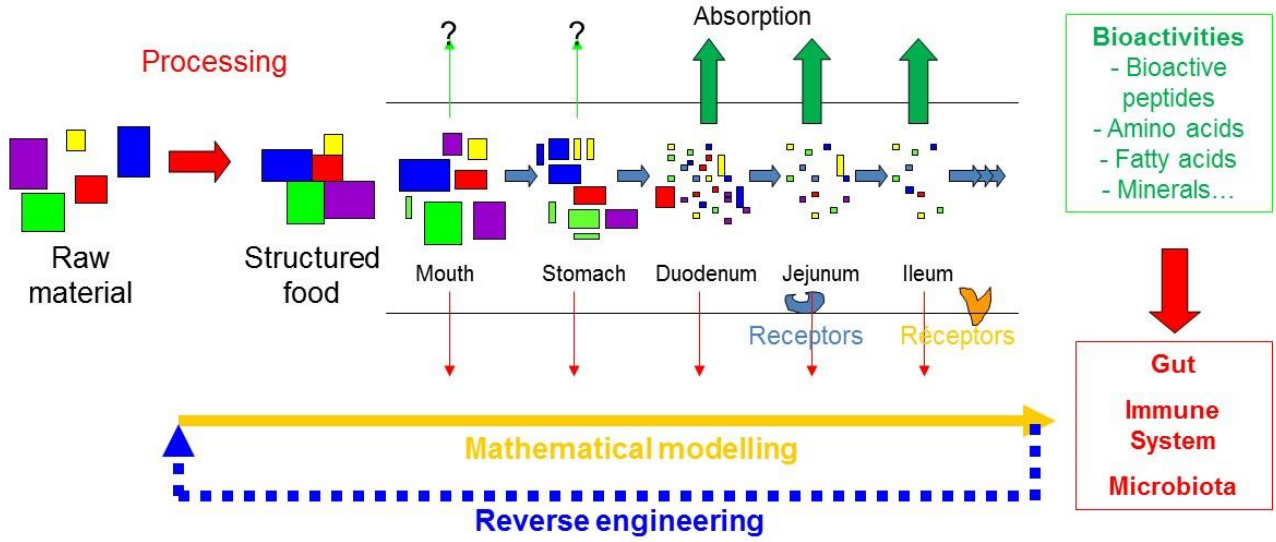

Processing
Raw material
Structured food
?
?
Absorption
Mouth
Stomach
Duodenum
Jejunum
Ileum
Receptors
Receptors
Bioactivities
- Bioactive peptides
- Amino acids
- Fatty acids
- Minerals…
Gut
Immune System
Microbiota
Mathematical modelling
Reverse engineering

Figure 1

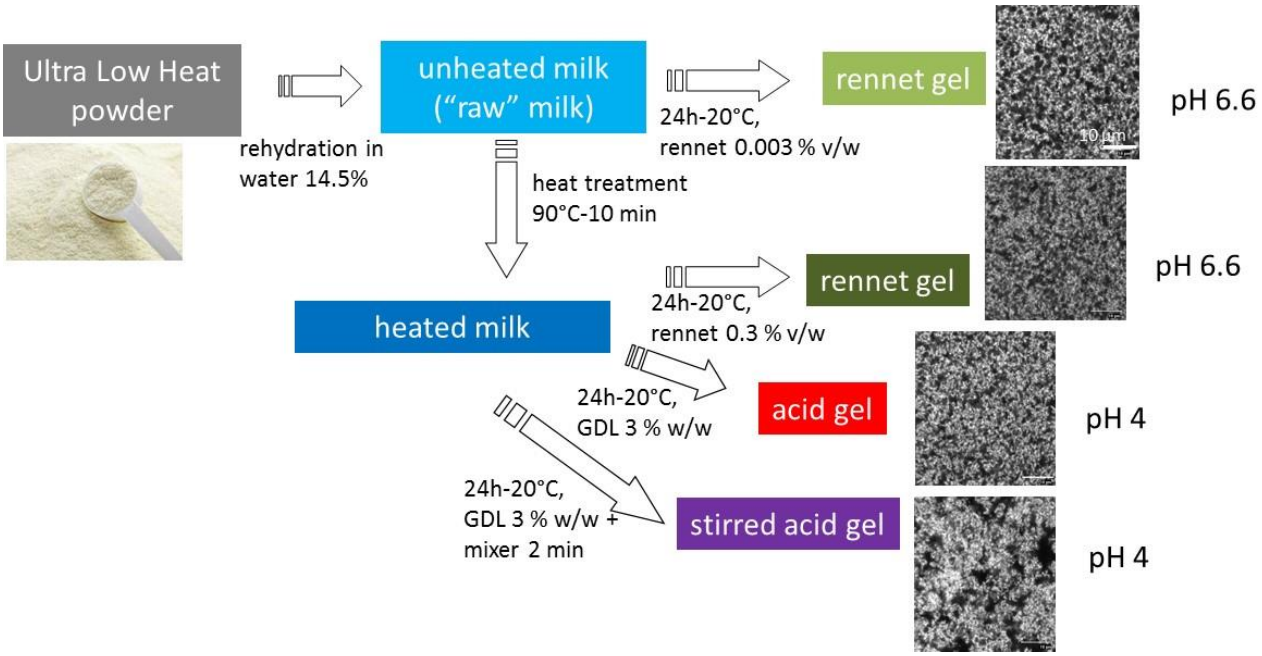
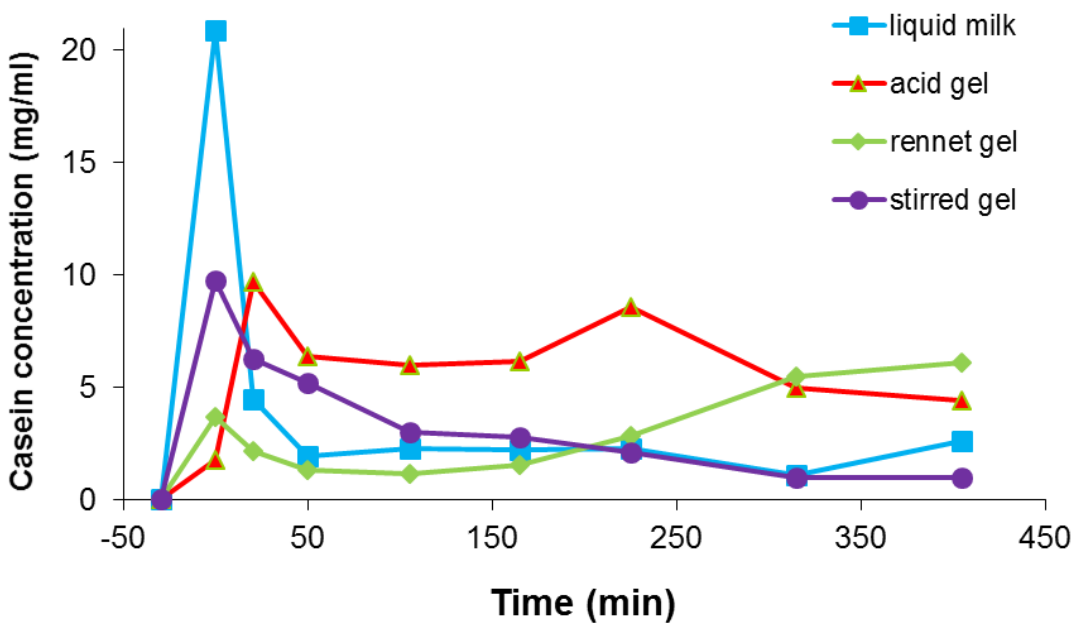

Ultra Low Heat powder
rehydration in water 14.5%
unheated milk ("raw" milk)
heat treatment 90°C-10 min
heated milk
24h-20°C, rennet 0.003 % v/w
rennet gel
pH 6.6
24h-20°C, rennet 0.3 % v/w
rennet gel
pH 6.6
24h-20°C, GDL 3 % w/w
acid gel
pH 4
24h-20°C, GDL 3 % w/w + mixer 2 min
stirred acid gel
pH 4

Figure 2


liquid milk
acid gel
rennet gel
stirred gel
Casein concentration (mg/ml)
20
15
10
5
0
-50
50
150
250
350
450
Time (min)

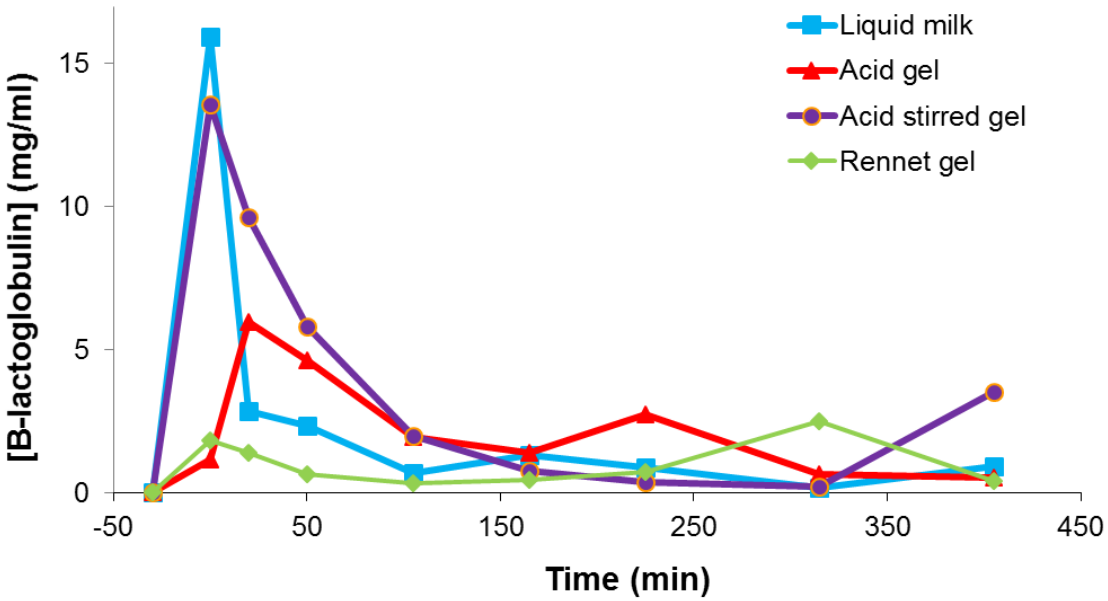

Liquid milk
Acid gel
Acid stirred gel
Rennet gel
[B-lactoglobulin] (mg/ml)
15
10
5
0
-50
50
150
250
350
450
Time (min)

Figure 3

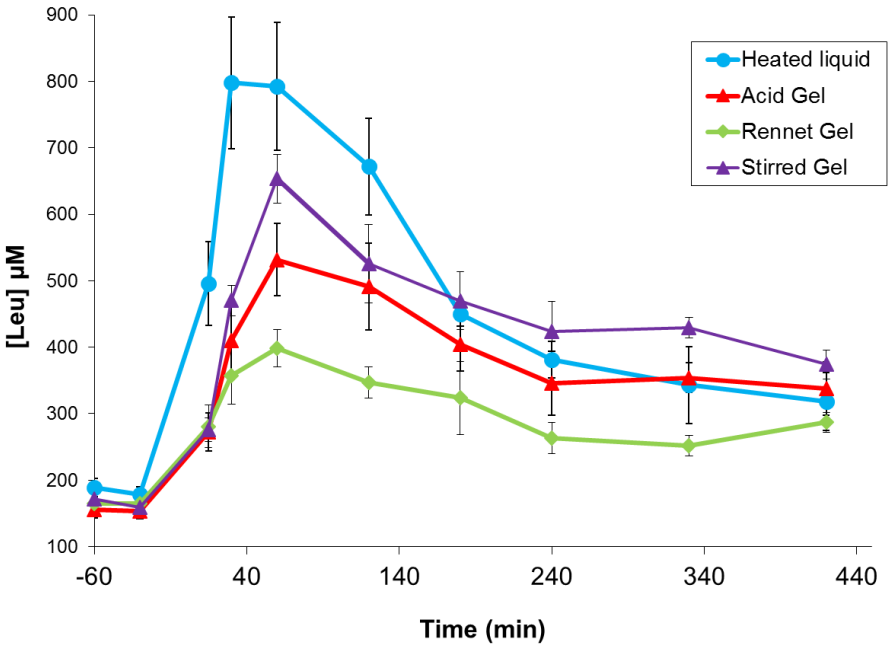

900
800
700
600
500
400
300
200
100
[Leu] µM
-60
40
140
240
340
440
Time (min)
Heated liquid
Acid Gel
Rennet Gel
Stirred Gel

Figure 4

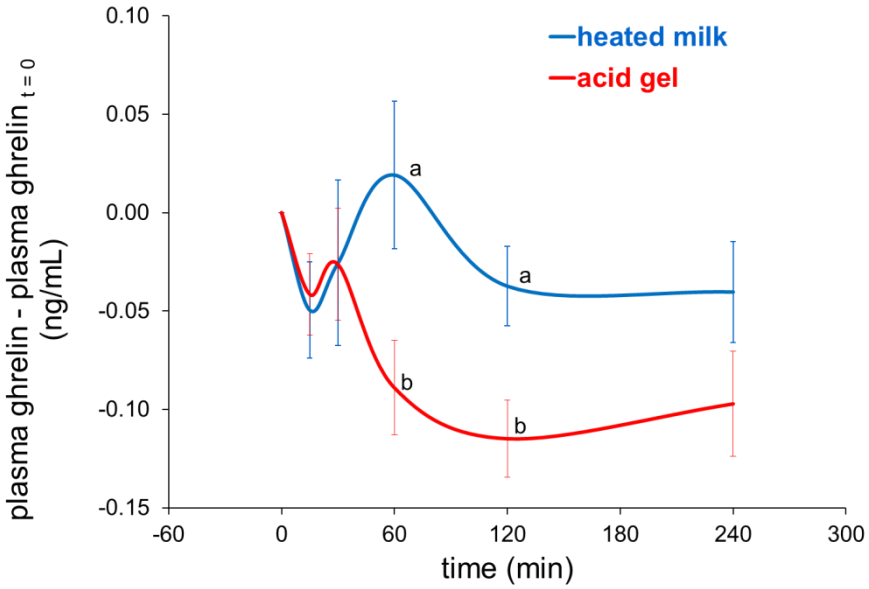
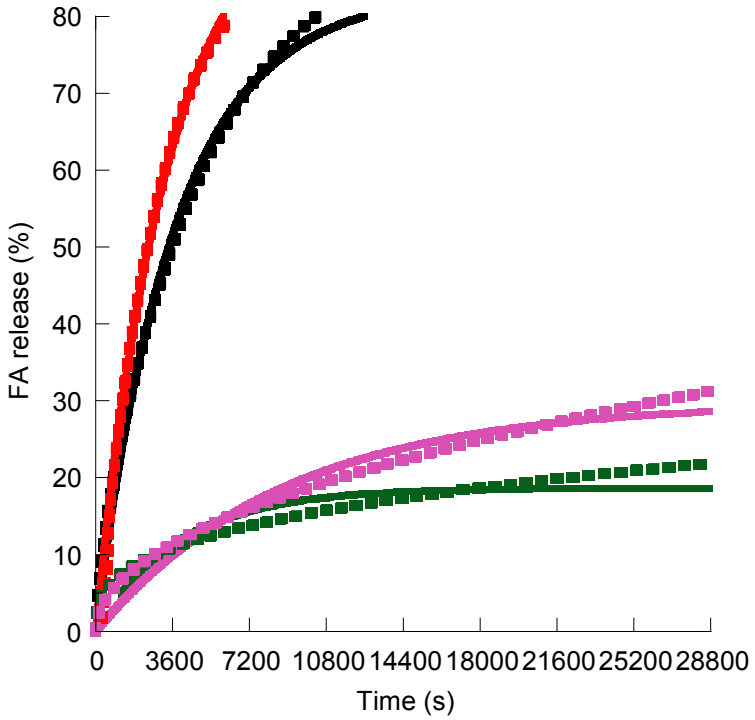

heated milk
acid gel
plasma ghrelin - plasma ghrelin t = 0 (ng/mL)
time (min)
0.10
0.05
0.00
-0.05
-0.10
-0.15
-60
0
60
120
180
240
300
a
a
b
b

Figure 5


80
70
60
50
40
30
20
10
0
FA release (%)
0
3600
7200
10800
14400
18000
21600
25200
28800
Time (s)

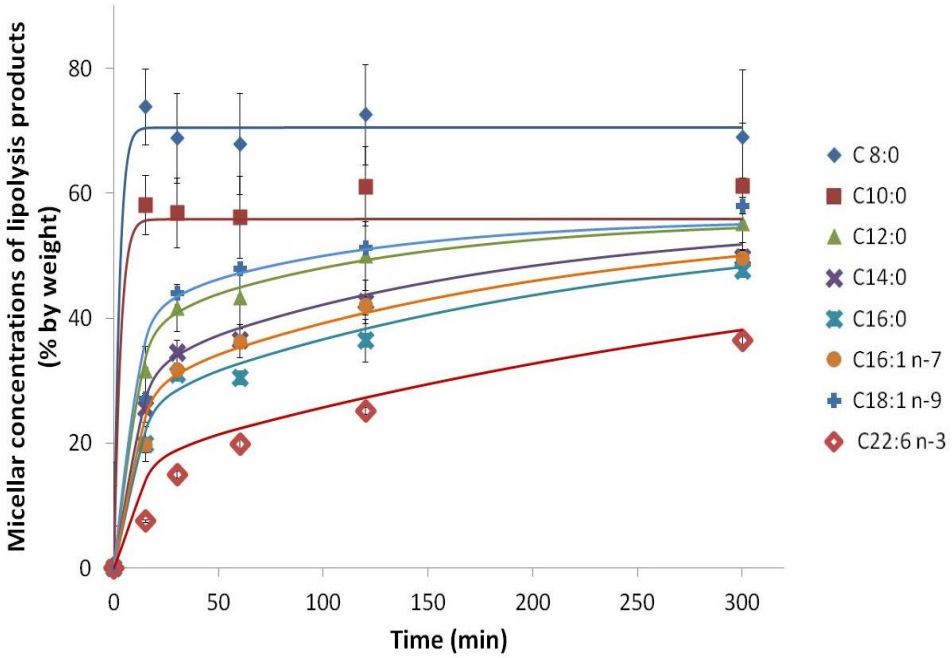

Micellar concentrations of lipolysis products (% by weight)
80
60
40
20
0
0
50
100
150
200
250
300
Time (min)
C 8:0
C10:0
C12:0
C14:0
C16:0
C16:1 n-7
C18:1 n-9
C22:6 n-3

Figure 7

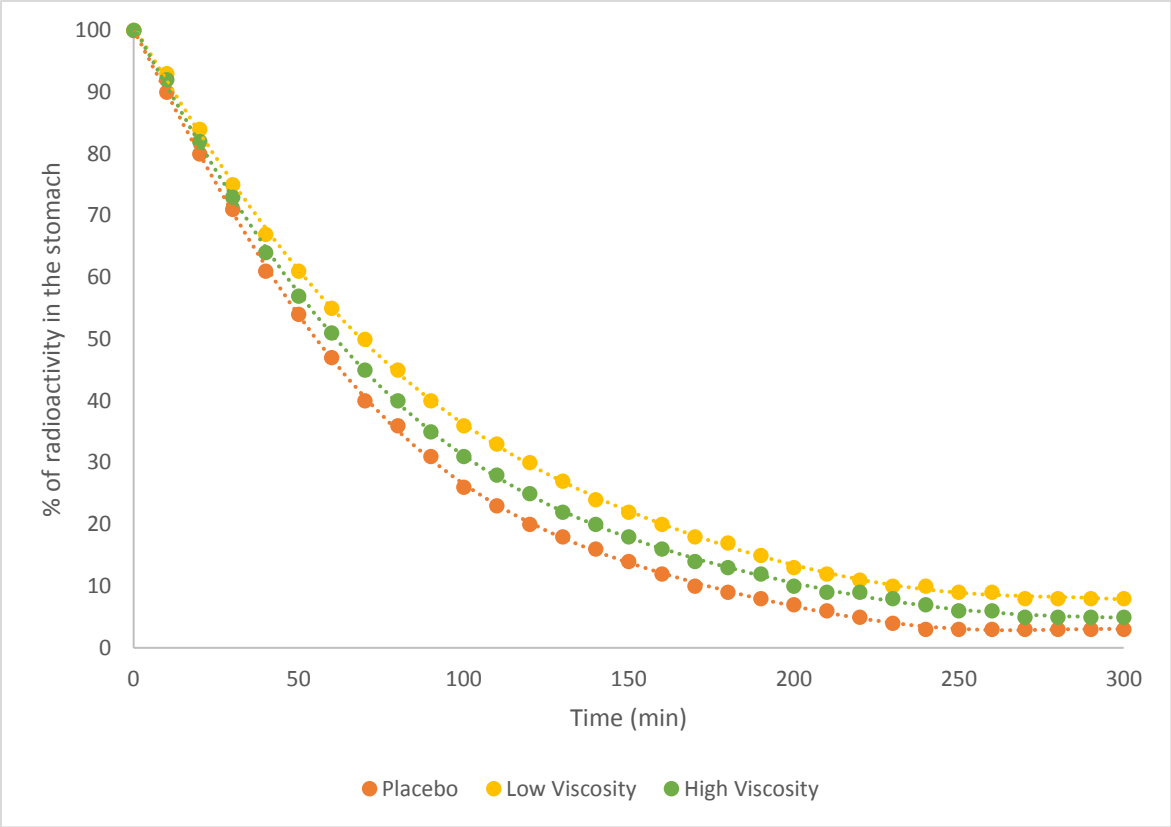

100
90
80
70
60
50
40
30
20
10
0
% of radioactivity in the stomach
0
50
100
150
200
250
300
Time (min)
Placebo
Low Viscosity
High Viscosity

Figure 8