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In Vitro Modeling of the Gastrointestinal Tract: Significance in Food and Nutritional Research and Health Implications

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Abstract

The aim of this communication is to highlight the significance of *in vitro* simulation of the human digestive system its impact on food and nutrition, and the application of nanoparticles in food systems. Many questions are being asked about the safety of Nanoparticles (NP) in foods. In as much as no specificity is given in terms of safety by regulatory agencies, one must appreciate the scientific effort underway to understand the interaction of nanomaterials, foods and the human digestive system and its impact on human health. Although, it must be noted that many decades ago, researchers developed numerous methods for testing food ingredients well before the advent of Nano-ingredients. Therefore, the knowledge and the capability predict the behavior of NP and its interaction with food in the stomach is significant for developing a novel product. Understanding the kinetics of nutrient uptake and the ensuing bio accessibility that occur during the pre-andpost-ingestion behavior of food is a prerequisite for processors to develop the ideal processing conditions and time for manufacturing. The advancement of bioprocess engineering techniques provides unprecedented opportunities to in building *in vitro* mechanical simulation model to mimic the GIT, hence many simulation models were built but much improvement is desired in almost all the available models for a more cohesive study of real foods behavior in the Gastrointestinal Tract (GIT) and its impact human health and nutrition.

Keywords: Control Release; Gastrointestinal Tract; *In Vitro*; Microbiota; Nanoparticles

Introduction

Interest in in the applications of Nanotechnology is growing in both the food and pharmaceutical industries. Its applications in the food industry are being experimented in the area of flavor control, textural enhancement, control release of nutrient and its bioavailability, and color enhancement. For examples the encapsulation of undesirable bioactive components in food, thus preventing the direct contact with the sensory organs during injection and hence sensory attributes in food remains intact with altering the properties is a typical application in in foods [1]. However, many questions are being asked about the safety of Nanoparticles (NP) in foods. In as much as no specificity is given in terms of safety by regulatory agencies, one must appreciate the scientific effort underway to understand the interaction of nanomaterials, foods and the human digestive system and its impact on human health. Although, it must be noted that many decades ago, researchers developed numerous methods for testing food ingredients well before the advent of Nano-ingredients [2]. For example, toxicity of titanium dioxide with particle size in the micro-scale was evaluated in the late 1960s on human cells and the safety limits for consumption was validated. Due to the limitation of technology, one may question the accuracy of the particles sizes measured then, hence may not underscore representation of the true value of the particles sizes. The safety protocols designed to test microscale ingredients may obviously not necessarily apply to the nanoscale food ingredients. It is a known fact that the physical properties are significant components associated to its safety.

Size and surface features can enhance or limit NP ability to penetrate cells. Some NP (including those considered safe by the FDA) may have negative effect on human cells [3,4]. For example, [3] reported the effects of silicon dioxide, titanium dioxide and zinc oxide on cells taken from the human intestinal linings. Their study revealed that at high doses (higher than what most people would ordinarily consume) of all the three NP tested were damaging to the human DNA, proteins and lipids in the cells, and zinc oxide was found to be the most toxic. However, at lower dose, zinc oxide was observed to impair certain proteins that aid in repairing damaged DNA, but cell death may occur at higher dose.

Although, it is not yet clear if NP has any toxic effects in the human gut, [5] alluded to the difficulty of classifying NP based on this toxicity or safety. Many studies that exposed human cells at high concentrations of NP have observed the effects on extreme cellular stress and in some cases cell death, hence the questions arise if those safety tests are appropriate method. There are efforts to study the effect of NP in food and it impact on the gastrointestinal tract (the mouth, esophagus, stomach and intestines) as shown in (Figure 1).

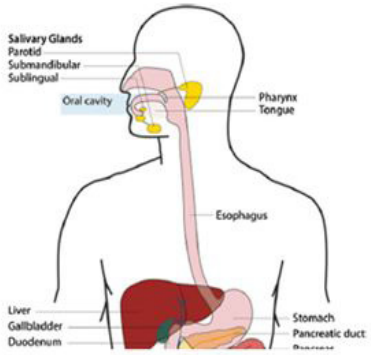

Figure 1 Illustration of part of the upper gastrointestinal tract (oral cavity and oesophagus). **Source:** Verhoeckx and Cotter [11]

Figure 1: Illustration of Part of the Gastrointestinal Tract (Oral Cavity an Oesophagus [11].

Nagy, et al. [6] studied the mass transport of NP in the digestive system of force-fed mice and their results revealed traces found in the liver, kidneys, lungs, brain and spleen of the mice. However, McClements [7] claimed that the NP studied was made from ingredients normally found in the human diet and the particles tend to breakdown during digestion in ways similar to foods. Some of these NP are expected to be safer than particles made of non-biodegradable materials, such as titanium dioxide. Therefore, many research hasrefocused their efforts to understand the relationship between consumption of food containing NP and the inherent nutritional benefits. The question still remains, could these NP find their way directly into the blood stream when consume, if it does, how will this impact human health.The results of the studies on NP have associated its physical characteristics such as: size, shape, material type, surface charge, solubility, and surface chemistry to its safe use and impact on human health. These characteristic properties are determinant factors to toxicity [8]. Furthermore, the condition in the GIT tract may also respond differently based on the characteristic nature of the NP [9,10], hence resulting in variations and modification of its biological effects [9]. However, many have suggested the impetus to study *in vitro*, the effect of physical properties of NP concurrently with in vivo models to validate the synergy of events that may imply some benefits otherwise adverse effect on human health.

On-a-daily basis, the Gastrointestinal Tract (GIT) is exposed to many different types of food components derived from meals. These could either be raw or processed, and when consumed it is eventually transported across the GIT and ensued with the requisite bio-physiological process that may direct and or indirectly impact human health. The in vivoassessments of the impact of food components (bioactive) on human health is not trivial but not practical, considering the variations of animal models to human system, while the human subjects for certain experimental purpose is limited by the Institutional Review Board (IRB). Therefore, it is imperative in many instances to employ *in vitro* and ex vivo models as part of a structured procedure to mechanically simulate and mimicking human intestinal digestive system. Thus, the aim of this communication is to highlight the potential of *in vitro* simulation of the human digestive system and its impact of NP in food on human health.

The *In Vitro* Simulation Model

The use of *in vitro* human intestinal models is widely used for evaluating the mechanistic effects of nutrient absorption and transport and extended to include the study of functional host-gut microbiome. The digestive tract in humans and other mammalian species are highly complex because of the natural phenomena that governs the efficacy of nutrients mobility and bioactive transport and absorption across the intestinal membranes and coupled with the control of pathogens and toxic compounds in foods consumed. While it is not easy to simulate this phenomenon, many efforts have led to the evolution of complex multilayered systems of control involving a number of distinct compartments to simulate the human GIT. These includes the oral compartment (mouth) where the initial sensory input from the food begins as shown in (Figure 1) [11]; the gastric compartment (stomach) where food is stored, partially digested and sterilized; the duodenum, jejunum and ileum (small intestine) which is the primary site for digestion and absorption of nutrients. Finally, the colon, which comprises of the proximal (ascending) colon, transverse colon and the distal (descending) colon as all part of the large intestine as shown in (Figure 2) [12]. Fermentation of the hydrolyzed indigestible polysaccharides such as resistant starches, soluble and insoluble fibers and proteins produces short fatty acids such as acetate, propionate, and

butyrate, branched chained fatty acid as well as lactate, formate, ethanol, and mixed gases (CH_4, CO_2 and H_2) [12,13].

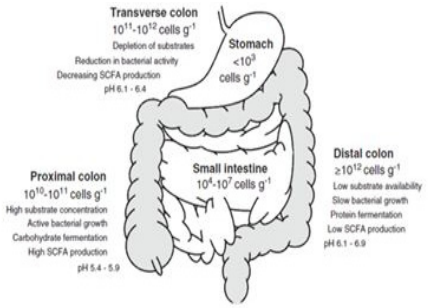

Figure 2 Illustration of the different component of the human gastrointestinal tract and the microbiome ecosystem. **Source:** Payne et al. [12]

Figure 2: Illustration of the Different Component of the Gastrointestinal Tract and the Microbiome Ecosystem [12].

Many different kind of mechanical simulation models were produces and the Simulator of the Human Intestinal Microbial Ecosystem (SHIME) is the sole model that integrates the entire GIT into a unique system as shown in Figure 3 [14]. The SHIME is the last generation of multi-compartment modules that operates in a semi-continuous (Chemostat) stirred tank bioreactors. Compared to other models, the SHIME is automated and computer controlled input and output streams of the chyme and other gastric medium cycling through the system at relatively controlled predetermined times, temperature and pH, thus offers greater advantage over other models [15].

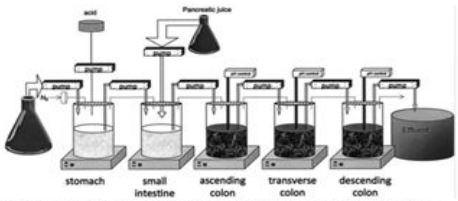

Figure 3 The schematics diagram of a simulator of the human intestinal microbial ecosystem. **Source**: van de Wiele et al. [14]

Figure 3: The Schematics of a Stimulator of the Human Intestinal Microbial Ecosystem [14].

The medium is usually composed of complex carbohydrate, proteins, some mineral and vitamin mixes and with the addition of mucins (mSHIME) [16]. The sequential digestion of (digesta=chyme) occurs in the stomach and the small intestine and subsequently pumped to the ascending colon (vessel=ascending colon) where initial stage of fermentation in the colon begins and hence proceeds into to transverse (vessel=transverse colon) and descending colon (vessel=descending colon) as shown in(Figure 2 and 3). Retention times of the chyme in the upper intestinal tract is modulated by rate of flow into the stomach and small intestine compartments, while by fluid volume in the colon. However, the retention time may vary from 24 to 72 h based on the subject of interest [17].

In Vitro Digestion of Nanoparticles

The GIT response to NP is different in many *in vitro* digestion models, the dissolution and aggregation characteristics are associated to the cause of toxicity, which is a unique postulation amongst the different models. The rate of dissolution could be used to modulate the toxic effect on the system [18]. For example, when silica NP was added to food matrices and subjected to *in vitro* digestion, it was reported to have significantly ($p < 0.01$) impacted the digestion and bioavailability of the bioactive components [18,19]. In the study the following conditions of digesta were used: saliva (pH 6.8), gastric juice (pH 1.3), duodenal juice (pH 8.1), and bile juice (pH 8.2) [18], an ensuing agglomeration of the silica was observed in the gastric digestion stage due to the low pH (the isoelectric point where silica is neutrally charged occurs at pH 2-3) and the high electrolyte concentration [18,19]. They also reported about 80% of E551 (Food grade silica) after full digestion in coffee was in the nano-size range (5-200 nm)[18].

In Vitro Microbiota

The interaction of NP and the gastrointestinal microbiota occurs mainly via ingestion of food emulsions, water, and or by topical applications of cosmetic. The microbiota is found in many site in the human body i.e., the oral cavity and GIT, hence majority of the microbial community are harbored in the later (Figure 2) and this has attracted many interest from diverse areas of research [20-22]. The GIT microbiota comprises of bacteria, fungi, viruses and archaea, and they basically form a complex ecosystem within the host [21,22]. The modulation of the ecosystem may lead to microbial imbalance (dysbiosis) hence renders the host susceptible to diseases. It offers several functions for the host, and this includes processing of indigestible food components, synthesis of phytochemical compounds, colonization resistance, regulation of the metabolism, and development of the immune system [20,23].

Human gut microbiota metabolizes nutrients and other compounds supplied through diet. In their experiment, [24] fed Rosmarinic Acid (RA) loaded NP in the GIT, and observed that the phenolic component of the constituent was not absorbed in the upper digestive tract but rather transported to the colon, where it undergoes hydrolysis by microbial glycosidases and esterases and eventual release of aglycones and some oligomers while enhancing their absorption in the colon [25]. However, very limited information is available on the effects NP on the gut microbiota health and its metabolic activities. In vivo and *in vitro* studies have shown that intestinal microbiota can regulate host lipid metabolism via numerous microbial activities [26]. The modulation of gut microbiota through diet to enhance host health was found to reduce the incidence of obesity and other associated disorders [27].

The evolution of the metabolic activities in the gut microbiota (*Universal, Firmicutes, Clostridium leptum, Lactobacillus,*

Roseburiahominis, Bacteroidetes, Bacteroides, Bifidobacterium) was observed during *in vitro* studies by [24], *Lactobacillus rhamnosus* GG [21] and *Bifidobacterium catenulatum, Enterococcus caccae* and *Ruminococcusgauvreauii*[22]. Based on 0, 8 and 24 h digestion study, analysis of the composition of the average numbers of copy by PCR real time was conducted by [24]. Three of the four dominant phyla in the human gut were evaluated, viz. *Firmicutes, Bacteroidetes* and *Actinobacteria* [28]. However, the unloaded NP was shown to negatively impact microbiota growth and cell viability, and in some cases the negative increment was much higher than the control, which implies bactericidal or toxic effects. However, in contrast the Loaded NP with RA induced growth of the Bifidobacterium and Lactobacillusgroups throughout the fermentation period. All NP loaded with herbal extracts had a positive effect on the growth of all the bacterial groups except *Roseburia* [24]. The most expressive growth (ca. 10-25%) was observed on *Bacteroides* in faeces with loaded NP. The results confirmed the notion that high fat diets reduce *Bacteroides* and *Bifidobacterium* group bacteria [29], because the unloaded nanoparticle is a solid with high concentration of lipid. Thus, the loading of NP with herbal extracts has tremendous health benefits.

Liu, et al. [30] tested three different sizes (10, 50 and 100 nm) of TiO_2-NP (TONP) on *Drosophila* intestinal commensal bacteria. The growth of *Acetobacteria* was not affected on selective plates containing 200 µg/mL of TONP, however, when the concentration was increased to 2 mg/mL inhibition of growth was observed. It was also observed that the *Enterobacteria* seemed to be more sensitive all sizes of TONP, because inhibition of growth was observed at much lower concentrations 2 to 200 µg/mL ($p < 0.05$), this was likewise observed on Lactobacilli. The NP sizes (50 and 100 nm) significantly inhibit *Lactobacilli* growth in both 200 µg/mL and 2 mg/mL, while 10 nm had limited effect. The results suggest that TONP can inhibit the growth of commensal bacteria *in vitro*, however their sensitivity to dosage and particle sizes differs [30].

Summary

In vitro modeling of the GIT offers limitless opportunities for ethical study of all aspects the GIT including the behavior of NP and its effect on the GIT microbiota and the ultimate impact on human nutrition and health. Although, much success was gain in the evolution of the *in vitro* GIT most, much improvement is desired to improve the current GIT simulation models to realistically mimic the human GIT. It must also be noted that without correlating the *in vitro* data against the in vivo, the results may lack the relevant credibility. Although, much complex, the cellular uptake of NP and its impact on the GIT microbiome required multidisciplinary between engineers, biologist and biotechnologist is much desired. The advancement of bioprocess engineering techniques provides unprecedented opportunities to advance new food processing techniques to enhance the nutritional content of foods. Provide new information that will lead the design of novel food products that will enhance the controlled release of bioactive compounds in the Gastrointestinal Tract (GIT), thus improving healthy consumption of foods.

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