Satiety, Weight Loss, and Glycemic Control-Enhancing Properties Vary Between Functional Fibers, Mixed Vegetables, and a Novel Hydrogel (Gelesis200)

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INTRODUCTION

- The importance of fruits, vegetables, and wholegrains as part of a healthy diet is well documented, in part because of their abundance of naturally occurring dietary fibers. Demonstrated benefits of dietary fibers relevant to the management of overweight and obesity include reduced appetite and energy intake, prolonged absorption of nutrients, and reduced body weight.[1]
- Ingestion of functional fibers and high-viscosity polysaccharides has been employed as a strategy to improve glycemic control, suppress appetite, and facilitate weight loss in patients with increased cardiometabolic risk.
  - Prospective studies suggest that consumption of fibers with higher viscoelastic properties were 2-4 fold more effective at reducing appetite and energy intake than fibers with lower viscoelastic properties.[1]
- Superabsorbent hydrogels are three-dimensional cross-linked polymer networks capable of absorbing much larger quantities of fluids compared to linear structures of functional fibers, thus resulting in more rigid, elastic gel particles **(Figure 1)**. Hydrogel technologies have been employed for a variety of therapeutic uses such as tissue engineering and enhanced drug delivery.
- Gelesis200 is a novel orally-administered, non-systemic hydrogel comprising a matrix of modified cellulose cross-linked with citric acid (both commonly used in foods; **(Figure 2)** that is designed to mimic the three-dimensional structure of naturally occurring dietary fibers in vegetables. While Gelesis200 utilizes a similar technology platform as Gelesis100, another hydrogel currently in clinical development for weight loss and glycemic control, the two hydrogels are engineered to exhibit reciprocal physical properties: Gelesis200 demonstrates a faster rate of hydration, yet a lower media uptake ratio (i.e., creates a smaller volume) than Gelesis100 **(Figure 3)**.
- The purpose of this study was to compare the viscoelastic properties of Gelesis200, which is currently in clinical development for weight loss and glycemic control, versus common processed functional fibers, vegetables rich with natural fibers, and Gelesis100.

Figure 1: Comparison of superabsorbent hydrogels and linear processed functional fibers.

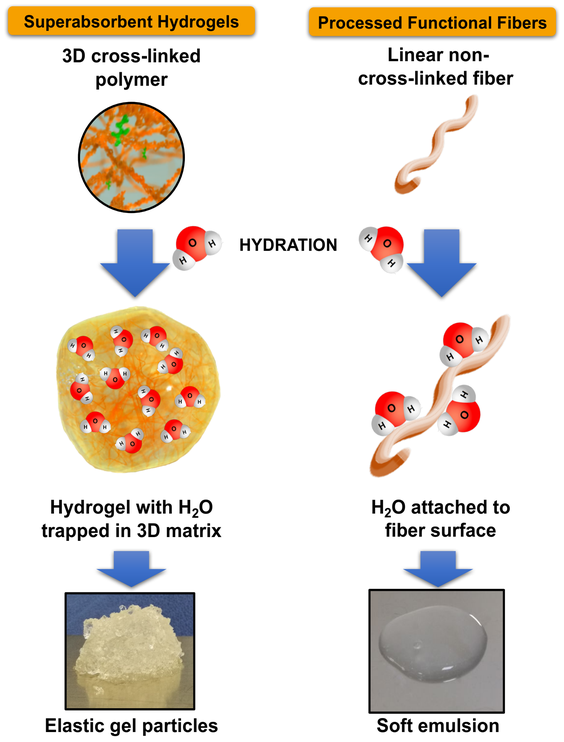


Figure 2: Gelesis200 is composed of modified cellulose (carboxymethylcellulose) and citric acid, both found in common foods.

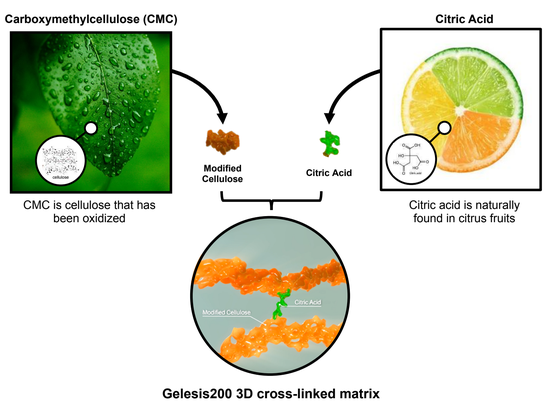
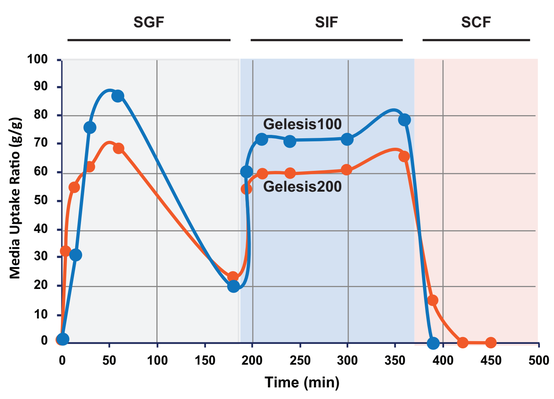


Figure 3: Differential hydration kinetics and capacity between Gelesis100 and Gelesis200, determined by simulated gastrointestinal fluid uptake ratios. SGF = simulated gastric fluid, SIF = simulated intestinal fluid, SCF = simulated colonic fluid.



METHODS

- Processed functional fibers (psyllium, guar gum, and glucomannan) and Gelesis200 were pre-hydrated in simulated gastric fluid (SGF)/H_2O 1:8 (V/V) media in a 1:160 (w/V) ratio, and vegetables (mixed salad greens, cucumbers) were subjected to mechanical mastication and then poured in SGF/ H_2O 1:8 (V/V) solution in the same amount.
- Ten grams of hydrated and masticated samples were subjected to serial *in vitro* digestion in simulated gastric, small intestine, and colonic fluids (as described in **Table 1**) for 30-180 min each at 37°C in a glass beaker under mild mechanical mixing. Remnants of digested samples were poured onto an AERS rotational rheometer (TA Instruments) equipped with parallel plates (cross hatched configuration) for determination of elastic modulus (G') in triplicate.

Table 1: Composition of simulated gastrointestinal fluids

Simulated Fluid	Composition per 1,000 mL	Approximate pH	Digestion Time (min)
Gastric (SGF)			
1/8X	0.25 g NaCl, 0.4 g pepsin	~2.1	30
1/4X	0.5 g NaCl, 0.8 g pepsin	~1.8	90
1X	2.0 g NaCl, 3.2 g pepsin	~1.2	60
Small Intestine (SIF)	6.8 g KH_2PO_4, 10.0 g pancreatin (trypsin, amylase, lipase, ribonuclease, protease)	~6.8	120
Colonic (SCF)	6.8 g KH_2PO_4, 10.0 g pectinase	~6.8	30

RESULTS

- **Gelesis200 vs. Processed Functional Fibers (Figure 4A and Figure 5)**
  - Throughout 180 min digestion in SGF, the G' of Gelesis200 (range: 1,301 ± 145 to 2,082 ± 35 Pa) was maintained orders of magnitude higher than glucomannan (range: 27 ± 2 to 49 ± 3 Pa), which had the highest elastic modulus of any functional fiber tested.
    - This pattern was maintained during 120 min digestion in SIF (range: 994 ± 139 to 1,220 ± 159 Pa for Gelesis200 versus 42 ± 2 to 50 ± 4 Pa for glucomannan).
      - While G' of glucomannan and guar gum were maintained during a final 30 min digestion in SCF, Gelesis200 lost its elastic modulus (G' < 10).
- **Gelesis200 vs. Vegetables (Figure 4B and Figure 5)**
  - Throughout digestion in SGF and SIF the G' pattern of Gelesis200 (range: 994 ± 139 to 2,082 ± 35 Pa) was remarkably consistent with that of masticated mixed salad greens (range: 105 ± 11 to 2,074 ± 101 Pa) and cucumber (range: 72 ± 11 to 6,493 ± 200 Pa), and all three lost their elastic moduli in SCF.
- **Gelesis200 vs. Gelesis100 (Figure 4C and Figure 5)**
  - During digestion in SGF and SIF, the G' pattern of Gelesis200 was maintained consistently higher than Gelesis100 (range: 257 ± 3 to 950 ± 10 Pa), and both lost their elastic moduli in SCF, which is consistent with degradation by esterases.

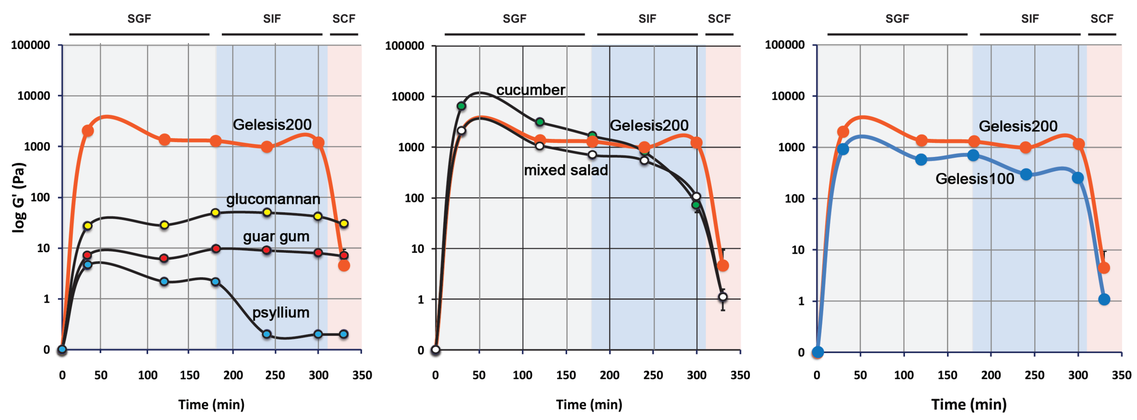


Figure 4: Comparison of elastic modulus between Gelesis200 and processed functional fibers (panel A), vegetables (panel B), and Gelesis100 (panel C). Data presented as log-transformed transformation of G' values in pascals.

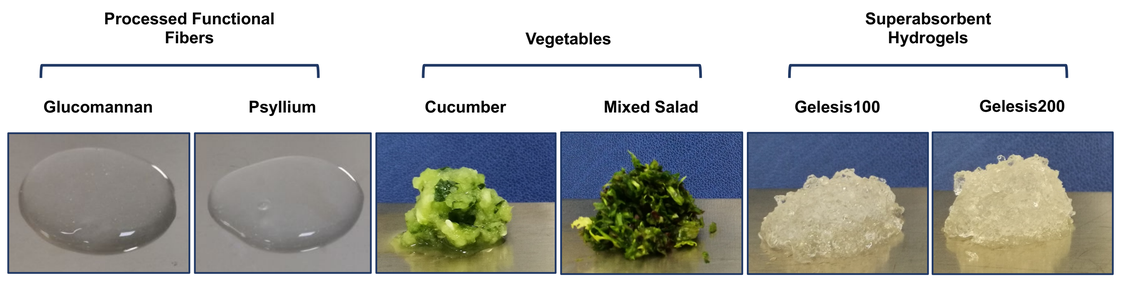


Figure 5: Visual comparison of processed functional fibers, vegetables, Gelesis200 and Gelesis100 following hydration and mastication.

DISCUSSION

- Although it has been long established that weight loss of 5 to 10% can lower the risk of weight-related comorbidities,[2] realization of this benefit from dieting is frequently derailed by biologic feedback mechanisms that stimulate appetite, reduce dietary compliance, and ultimately lead to a rebound of energy intake and weight gain.[3] Consequently, this has prompted efforts to understand how and to what extent eating behavior, digestion, and metabolism are influenced by the rheological properties of food and/or food additives, in addition to their inherent caloric value and macronutrient composition.[4,5]
- Several properties of natural fibers, including viscosity and elasticity, appear to confer benefits of appetite control and weight loss.[1] However, less than 3% of individuals in the United States consume recommended amounts.[6] Thus, efforts to compensate for inadequate dietary intake include supplementation with processed functional fibers which have linear structures that have lower viscoelastic properties.
- In this *in vitro* model of GI digestion, Gelesis200 and Gelesis100 demonstrated viscoelastic profiles that were orders of magnitude superior to that of common processed functional fiber supplements (psyllium, guar gum and glucomannan), and were remarkably similar to the profiles of the masticated vegetables tested. This latter observation is consistent with the components and structure of the hydrogels **(Figure 2)**, which when hydrated in the GI system, results in individual gel particles that are fluid-containing 3D cellulosic matrices, akin to plant cells.
- Increasing the elasticity of ingested meals has been shown to increase feelings of fullness in humans.[7] Similarly, acute dosing of Gelesis200 in humans increased subjective feelings of fullness and satiety in subjects who were overweight and had obesity **(ECO Abstract #937)**, and chronic dosing of Gelesis100 elicited weight loss and improved glycemic control.[8] The data observed in this study provides *in vitro* mechanistic evidence for these phenomena in humans, and suggests that Gelesis200 may induce feelings of satiety and fullness by mimicking the physical properties of ingested vegetables.

CONCLUSIONS

- In this *in vitro* model of GI digestion, Gelesis200 and Gelesis100 demonstrated viscoelastic profiles that were similar to masticated vegetables, and were orders of magnitude superior to that of common processed functional fiber supplements. The reciprocal hydration and viscoelastic properties of the two hydrogels suggest a potential for different therapeutic applications.
- These data provide evidence that Gelesis200 and Gelesis100 mimic the physical properties of ingested vegetables, which may in turn confer satiety-inducing, weight-loss, and glycemic-control benefits to patients with obesity or diabetes.

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