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Edible hydrogels with shrinkage tolerance in acids and stomach-friendly mechanical moduli

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ABSTRACT

Healthcare devices for the human body have seen continuous evolution, from external wear to wearables, and now to entirely concealed placements. The gastrointestinal (GI) tract offers considerable surface area for medical device introduction. In particular, hydrogels have been explored for disease treatment, specifically for long-term gastric retention to aid in bodyweight control. The current method of oral administration of hydrogels is challenged by two problems, namely, non-edibility and low shrinkage tolerance in acids, which prevents their practical application. In this paper, a new type of edible natural polymer-based hydrogel possessing a desired balance of swelling behavior in both neutral and acidic environments is introduced. Results based on animal experiments have shown that these edible hydrogels are a safe and efficient method for bodyweight control. The new edible material offers advantages for healthcare applications in the GI tract.

1. Introduction

Advances in materials and devices are transforming the landscape of the healthcare industry. New medical technologies can range from miniature implantable devices (e.g., deep brain stimulators for Parkinson's diseases [1]), which are normally made from bulky and conventional semiconductor materials, to skin-based epidermal devices enabled by thin and flexible electronics [2–4], to transient devices based on bio-resolvable materials [5–7], to ingestible and edible devices that use food-based materials or hydrogels [8–11]. In sum, devices are rapidly transitioning from external to wearable to entirely concealed components. As the primary interface between the internal milieu and the external environment, the gastrointestinal (GI) tract offers tremendous surface area for device residency to enable health condition monitoring [12], drug delivery [13], and disease intervention [14], and more specifically treatment for body weight control and obesity [15]. In addition to regular physical exercising, dieting, pharmacotherapy, and bariatric surgery (e.g., gastric bypass and other weight-loss surgeries), intragastric balloon is emerging as a new method to treat obesity. Intragastric ballooning involves placing a saline-filled balloon made of polyurethane (Garren-Edwards Gastric Bubble) or silicone (Orbera™, Obalon®, and ReShape®) in the stomach for an extended period of time (up to six months) to limit the amount food intake and to make patients feel fuller sooner. A surgical procedure, endoscopy, is performed for the placement and removal of the intragastric balloon, which is often expensive and involves the patient being sedated. The side effects can range from nausea to serious complications, such as balloon deflation and the deflated balloon moving through the patients' digestive system, which then will need to be removed by an additional surgical procedure. Hydrogels, on the other hand, are seen as potential alternatives due to their similar physical properties to human tissue, and more specifically, their fast and large swelling ratios in addition to controllable deswelling upon certain stimuli [10].

Orally administrated hydrogels have two problems that prevent them from practical applications [1]: synthetic polymer-based hydrogels [10] are non-edible, and [2] many hydrogel, such as most natural polymers or restricted edible (e.g., polyacrylate sodium) or even non-edible (e.g., polyacrylamide/polyacrylonitrile) all exhibit poor swelling behavior in acids because of the ion screening effect applied on polymer networks [16]; however, the stomach presents an acidic environment (e.g., pH ranges from 0.9 to 2.2 under the fasted state [17]). For example, polyacrylate sodium swells hundreds of times in deionized (DI) water, but shrinks to only a dozen times in pH = 1 solutions [18], presenting low shrinkage tolerance in acids. Natural polymer-based hydrogels can hypothetically resolve the problem of being non-edible though they also bring another challenge, namely, inherent poor swelling ratios (about 5 ~ 50) even in DI water due to their relatively rigid polymer chains compared with flexible ones for the synthetic

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polymers. Chemical derivatization of natural polymers (e.g., grafting of anionic groups) is a commonly used option to enhance swelling ratio. While this severely restricts the edibility factor, resulting in only a small fraction of these natural polymers (e.g., carboxymethyl cellulose sodium, starch acetate) being permitted for dietary use, or does not exhibit satisfactory shrinkage tolerance in acids. For example, the carboxymethyl cellulose sodium and citric acid based medical device that was recently cleared by US Food and Drug Administration (FDA) had roughly 20 times and 90 times swelling ratios respectively, in pH = 1 and PBS solutions [19,20]. Overall, the edibility and adequate shrinkage tolerance in acids for most existing hydrogels is yet to be satisfied.

Here, we introduce an edible natural polymer-based hydrogel with good shrinkage tolerance in acids as potential material for intragastric retention application. Marine resource exacted chitin and its derivatives are found to have anti-adipogenic effects which can be used to treat hyperlipidemia and fatty liver that are highly relative to obesity [21–23]. The hydrogel was synthesized through a process of randomized condensation of ethylene glycol diglycidyl ether (EGDE) and guanidine hydrochloride monohydrate (GuHCl·H_2O) on chitin molecules. Use of EGDE as the crosslinker remarkably enhances the swelling ratio, and the guanidine component in GuHCl·H_2O endows the hydrogel with favorable shrinkage tolerance in acids. Rigid chitin nanofibers form the skeleton of the polymer network and act as the substrate for chemical grafting of EGDE molecules. The swelling ratio of the hydrogel is over 300 (for bulk) and 600 (for powder) in DI water, and about 50 (for bulk) and 80 (for powder) in pH = 1 solution, respectively, presenting a good balance of swelling behavior in both neutral and acidic environments. We also conducted animal experiments using mice and rats to demonstrate the developed edible hydrogels as safe and an efficient use for bodyweight control. Up to 25% reduction in weight growth compared with the control group was observed for the rat model. This work presents a new edible material that offers advantages over existing synthetic polymer-based hydrogels due to its unique edibility and high shrinkage tolerance in acids, thus representing a significant advancement in material choice for healthcare technologies.

2. Results

2.1. Material synthesis strategy to achieve edible hydrogels with shrinkage tolerance in acids

Fig. 1a illustrates the chemical reaction leading to edible natural polymer-based hydrogels with three key components: chitin, GuHCl·H_2O, and EGDE. Chitin, which is a polysaccharide from the skeleton of many marine resources, has been used in the food industry, and its chemical derivative chitosan can swell to high levels and even dissolve in acidic solutions because of its amido groups (-NH_2) with protonation ability acting as a stabilizer against acid-induced shrinkage. Guanidinium groups in GuHCl·H_2O hold an intriguing capability of protonation in even alkaline solution [24], which endows the guanidine-based polymers with immense potential for proton affinity and swelling capacity in weak acidic environments, acting like chitosan [25,26]. EGDE, as an effective epoxy crosslinker, can react with the hydroxyl groups through ring-opening, which is commonly adopted in the preparation of highly swollen hydrogels [27]. In the reaction, chitin dissolves in the KOH/urea solution, and then mixed with GuHCl·H_2O and EGDE sequentially, where the KOH/urea solvent provides very strong alkalinity and brings self-condensation of epoxy groups [28], resulting in EGDE self-polymerizing to poly (ethylene glycol diglycidyl ether) (PEGDE) oligomers as well as crosslinks with chitin through etherification between the hydroxyl group on chitin and the epoxy group on EGDE under alkali catalysis. Meanwhile, ring-opened epoxy

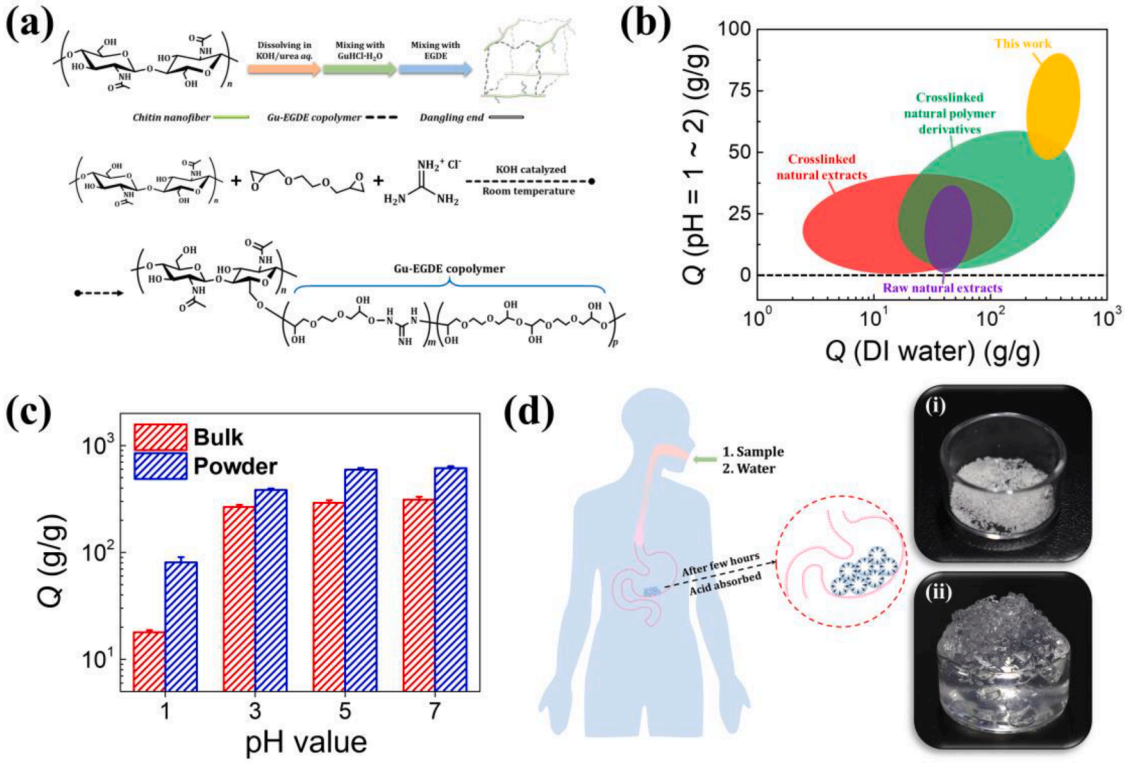

Fig. 1. Synthesis strategy of natural polymer based edible hydrogels with tolerance in acids. (a) Schematic diagram of the preparation process of GuChE copolymer, including the dissolution of chitin and reactions between chitin, guanidine, and EGDE under alkali condition. (b) Comparison of the swelling ratio *Q* in DI water and acidic solution (pH = 1,2) among known edible hydrogels (i.e., raw natural extracts [44–47], crosslinked natural extracts [48–53] and crosslinked natural polymer derivatives [53–58]). (c) Swelling ratio *Q* of GuChE 10–1–7.5 in bulk and powder forms under different pH value (25 °C). (d) Application of GuChE in gastric volume occupation. The optical images show the fully swollen state (ii) of the GuChE 10–1–7.5 hydrogel in pH = 1 solution (37 °C, $Q \sim 80$) from dry powder (i).

groups tend to react with amine groups on guanidine under alkali catalysis [29]. which has been utilized in the preparation of antibacterial materials [30,31]. In the synthesized hydrogels, chitin nanofibers function as the backbone and the randomly condensed Gu-EGDE copolymer elongates the length of the crosslinker in order to enhance the swelling capacity and stability in acidic solutions. The synthesized edible hydrogel is referred to as GuChE, and its chemical structure is shown in Fig. 1a. Spectrum analysis in Fig. S1 and S6a shows the successful grafting of guanidine and EGDE components on chitin molecules. Specifically, XRD results show that the synthesized hydrogel does not have a good crystal structure ensuring its swelling behavior, while chitin shows its well-defined crystal structure that leads to poor swelling capacity. The swelling ratio Q of GuChE sample strongly depends on the initial dose of chitin, EGDE, and GuHCl·H_2O, as shown in Table. S1, where the highest swelling ratio occurs when the initial weight ratio of the three chemicals (i.e., GuHCl·H_2O, chitin, EGDE) is 10:1.0:7.5, marked as GuChE 10–1–7.5. Moreover, after consumption of the hydroxyl groups of chitin molecules, excessive EGDE and GuHCl·H_2O may form Gu-EGDE copolymers as dangling chains along with the chitin backbone (Fig. 1a). This would help to capture water molecules more easily compared to raw chitin, and thus endow a higher accessibility to swelling.

Fig. 1b shows the shrinkage tolerance of GuChE in acids through a comparison of the swelling ratios in DI water and pH = 1 to 2 solutions for known edible hydrogels as administrated by US FDA or its counterparts in different countries/regions; this includes raw natural extracts (e.g., cellulous, chia seed extract) in purple, crosslinked natural extracts (e.g., chitosan crosslinked with glutaraldehyde) in red, crosslinked natural polymer derivatives (e.g., carboxymethyl cellulose crosslinked with epichlorohydrin) in green, and the present work in orange. A significant deterioration on swelling ratio in pH = 1 solution is observed in all samples. Specifically, the present GuChE hydrogel possesses the lowest ratio of deterioration of about 6, while in the case of crosslinked natural polymers and their derivatives, this ratio ranges from 10 to even 100, showing a weaker shrinkage tolerance in acid. Clearly, the present work shows the most superior swelling behavior in both DI water and in acids. Fig. 1c further presents the pH-dependence of the swelling ratio of GuChE 10–1–7.5 in bulk and powder forms. Though the swelling ratio drops from over 300 (for bulk) or 600 (for powder) in the DI water to about 20 (for bulk) or 80 (for powder) for pH = 1 acidic solution due to the protonation of polymer chains which leads to neutralization and loses swelling ability [32,33], compared with known edible polymers, the GuChE hydrogel exhibits much better shrinkage tolerance in acids, possibly owing to a more stiff polymer network against excess shrinkage. Here, GuChE in powder form presents a significantly higher swelling ratio than that in the bulk form because the former has a large specific surface area and exposes abundant hydrophilic functional groups for bonding more water molecules. Moreover, higher deformability of the hydrogel cluster integrated by hydrogel powders would better adapt the gastrointestinal shape and

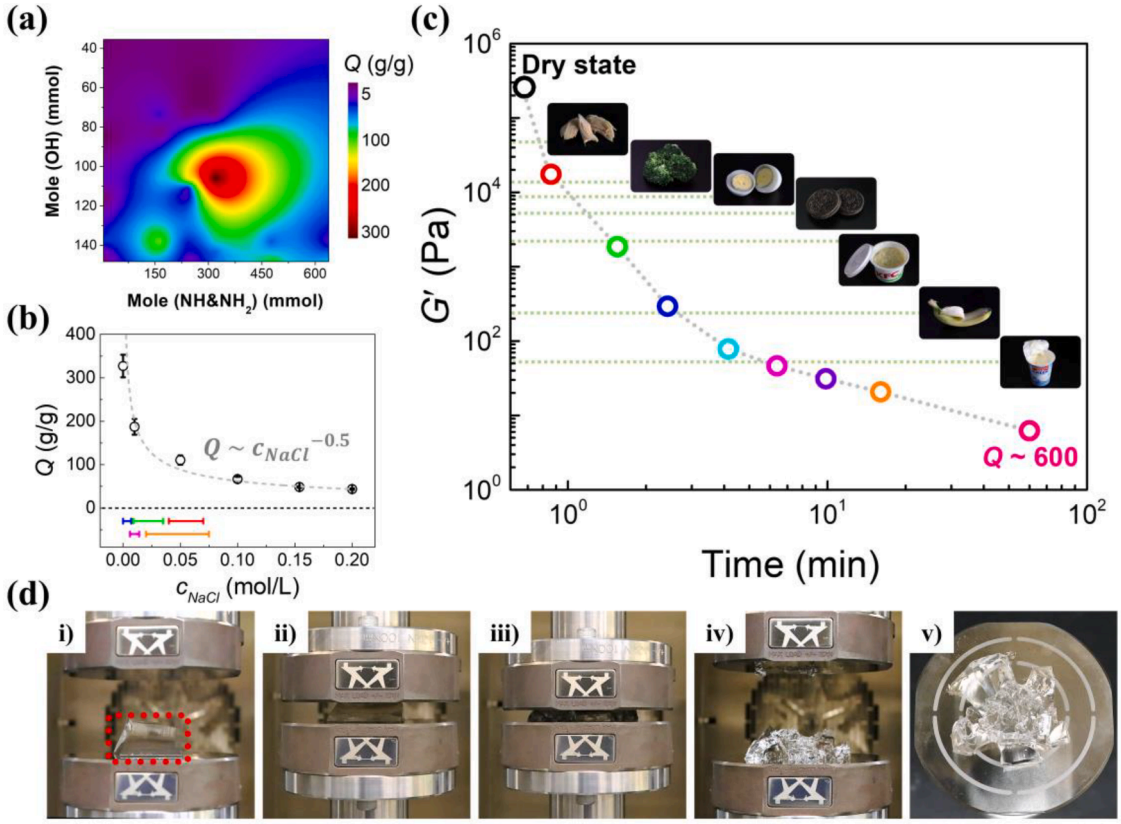

Fig. 2. Swelling ratio and mechanical properties of the GuChE hydrogel. (a) Phase diagram of the swelling ratio Q of the GuChE hydrogel in bulk form in 25 °C for 24 h, depending on moles of the amine groups (primary and secondary amines) from chitin and GuHCl·H_2O, and the hydroxyl groups from chitin and that produced by EGDE ring-opening. (b) Swelling ratio of GuChE 10–1–7.5 in the bulk form under different NaCl concentration (25 °C, 24 h). Color segments refer to the salt concentration range of common foods with red for noodle soups, green for vegetable soups, blue for vegetable dishes, magenta for yogurt, and orange for pasta sauce. (c) Storage moduli G' of GuChE 10–1–7.5 in powder form varies with swelling time at 37 °C. The G' value was collected at $\omega \approx 0.3$ rad/s, similar to the gastric motility. The Q values of each datapoint (start from the left) was 0 (dry state), 10, 50, 100, 200, 300, 400, 500 and 600, respectively. The moduli of common foods in chewed form (i.e., boiled chicken breast, boiled broccoli, boiled egg, cookie, smashed potato, banana, yogurt) are provided as a reference. (d) Fracture process of a relatively tough GuChE hydrogel under compression: (i) strain = 0%; (ii) strain = 50%; (iii) strain = 80%; (iv) stress removed; (v) top view of the fractured hydrogel. Red dashed line indicated the unbroken hydrogel.

avoids any block during hydrogel transition and excretion. It is noted that the pH of human gastric fluid in the fasted state is typically below 2 while increasing to about 4 to 7 after water and food intake [34], suggesting that the GuChE hydrogel is able to swell in the human stomach with a swelling ratio between 300 and 600 after hydrogel and water intake. Consequently, the potential application of the present edible hydrogel with high swelling behavior in weak acidic and neutral conditions as an intragastric volume occupant, particularly in its powder form, is highly feasible, as demonstrated in Fig. 1d. Here Fig. 1d (i) and (ii) show the photographs of a handful GuChE powders (dried) and its fully swollen state in pH = 1 solution.

2.2. Material characterizations: swelling and mechanical properties

The amido/imido groups in chitin and GuHCl·H_2O, and the hydroxyl groups from chitin and the ring opened EGDE govern the swelling behaviors of the edible hydrogels in water and acids. In Fig. 2a, swelling ratios for GuChE in bulk form in DI water are presented as the function of the initial dose of amido/imido groups from chitin and GuHCl·H_2O, and the hydroxyl groups from chitin and the ring opened EGDE. The swelling ratio is seen as reaching its maximum when the initial molar ratio of amido/imido groups and hydroxyl groups is about 3:1. In addition to pH-dependent swelling ratio, the ionization of amido and hydroxyl groups also affects the swelling ratio of the hydrogel in NaCl solution. Fig. 2b shows the salt-dependent swelling ratio of GuChE 10–1–7.5 hydrogel in bulk form, where the hydrogel shows a striking sensitivity due to the easily charged guanidine groups. Its swelling ratio decreases almost exponentially with an index of −0.5 as the salt concentration. The significant shrinkage of GuChE hydrogel in salt solution is similar to other hydrogels especially the polyelectrolytes [35–37]. By comparing with the salt concentration of some common foods in the daily diet (also shown in Fig. 2b), one can find that the salt sensitivity of the swelling ratio provides a fast way to intentionally shrink the swollen hydrogel by taking certain foods; they also serve as a guideline to avoid some foods (e.g., pasta sauce) for unintentional shrinkage of the hydrogel. One can expect that when it comes to practical application of the GuChE hydrogels for bodyweight control, salt intake should be prescribed by the physician to fully utilize the swelling behavior of this hydrogel.

Two mechanical properties matter for the edibility of the hydrogel [1]: mechanical stiffness (or modulus) as compared with common foods, and [2] water bondability under pressure (e.g., due to gastric motility). Fig. 2c compares the storage moduli G' of GuChE 10–1–7.5 hydrogel during the swelling process (i.e., from dry to fully swollen states) with common chewed foods, such as chicken breast, broccoli, boiled egg, cookie, smashed potato, banana, and yogurt, where G' was measured using a rheometer at frequency $w \approx 0.3$ rad/s (i.e., gastric motility frequency). More detailed data is shown in Fig. S2. The present edible hydrogel shows a comparable modulus of 40 Pa ($Q \sim 300$) as that of yogurt, indicating possible suitability of the edible hydrogel to the stomach. It is reported that satiety has a direct relation to the modulus of food, meaning the higher modulus the better satiety. Matching the modulus of food is able to control appetite and manage calory intake, which is very important to obesity treatment. To identify the water bonding property, a relatively tough GuChE 5–1–5 fully swollen hydrogel is compressed a way to observe its fracture process (Fig. 2d) and to mimic the cyclic compressive force due to gastric motility. It is seen that the hydrogel hardly releases absorbed water, neither under high compression nor after breaking, suggesting the adsorbed water is chemically bonded and retained by the polymer network, which is mainly contributed by abundant hydrophilic groups on the macromolecules. Combined with the high deformability of the powder form, the hydrogel is able to undergo gastric shearing and sustain the polymer network integrity. Notably, low modulus of the hydrogel at high swelling ratio can be mixed and excreted with food which maintain satiety for 18 to 24 h depending on the individual digesting period, which is aimed to avoid any long-term discomfort to the stomach, especially to the patients with gastrointestinal symptoms (e.g., gastritis) whose stomach are sensitive and feel uncomfortable after food intake.

Swelling speed is another important factor for edible hydrogels. Fig. 3 shows the time-dependent swelling behavior of GuChE 10–1–7.5 under different solutions and packages, in both bulk and powder forms. Fig. 3a shows the swelling dynamics of the bulk and powder hydrogels in DI water. Here, the dry powder has an average diameter of 300 mm. In DI water, the powder hydrogels exhibit around two orders of magnitude faster swelling speed than that in the bulk forms, specifically reaching 40% and 80% of the maximum swelling ratio in just 5 and 20 min for powder hydrogels, and 60 and 360 min for bulk forms, respectively. Fig. 3b shows snapshots of the powder and bulk hydrogels for Fig. 3a. For the sake of presentation, the dry powder hydrogels mixed with grinded sugar as dispersant are placed in an elastic balloon with initial size of about 0.8 cm in diameter made of a 120 mm thick Ecoflex membrane (Ecoflex 0030, modulus around 20 kPa) with about 450 mm pores for solution transport; the initial volume is about 0.27 cm^3 while the bulk hydrogel has an initial volume of 0.03 cm^3. In just 2 min, the elastic balloon filled with powder hydrogels swells to a much larger balloon with a diameter of 2.0 cm and reaches its maximum size of 3.2 cm in a diameter (i.e., ~ 100 times swelling ratio) in 20 min. The bulk hydrogel shows a much slower swelling speed, reaching swelling ratio of 300 after 24 h. It is also noted that the elastic balloon reduces the maximum swelling ratio of the powder hydrogels, compared with the powder hydrogels in the free form. Supplementary Video S1 and S2 further shows the swelling dynamics for the powder hydrogels in free form and in the elastic balloon. Fig. S4 and Supplementary Video S3 shows the Tyndall effect of fully swollen powder hydrogels ($Q \sim 600$), proving no excess water remains after fully swelling. The fast-swelling dynamics of the hydrogels in powder form is attributed to the larger specific surface area, allowing the hydrogel contact with more water at the same time and leading to a faster initial adsorbing rate.

The fast-swelling behavior of the powder hydrogels suggests a legitimate application for in-time gastric occupation. The swelling dynamics in saline (0.154 mol/L) is also provided in Fig. 3a, where its swelling speed is obviously slower and reaches equilibrium at 24 h. Fig. 3c shows the swelling dynamics of the hydrogel in acidic solutions and saline in the powder form, as compared to that in the bulk form, in which a similar trend as in Fig. 3a is observed, i.e., fast swelling speed and larger swelling ratio. Specifically, the powder samples (in green and black lines) showed faster swelling dynamic than the bulk samples (in purple line) and result in a faster swelling equilibrium. However, as indicated in Figs.1c and 2b, the ion concentration reduces the swelling ratio exponentially; hence, the final swelling ratio of the sample in pH = 1 and saline are significantly lower than that in pH = 5. Also, the ion concentration of pH=1 solution is smaller than saline, which swelling dynamic is a bit faster. Another interesting phenomenon is that the pH value of the solution varies as the edible hydrogel swells. As shown in Fig. S3, the swelling of GuChE 10–1–7.5 leads to an increase in the pH of the solution, from the initial pH = 5 to 6.5 after 3 h and eventually to 7 at the fully swollen state, showing a neutralizing effect due to the guanidine component with a favorable proton affinity (Fig. S3). Since the personal daily nutrition intake is different from each other (different types and amounts of sugars, proteins, fats, salts and dietary fibers), the composition of the chyme is difficult to identify, hence we only consider the major effect, that is pH value and ion concentration to the swelling of the hydrogels in this work.

2.3. Edibility and efficacy studies of the edible hydrogel using animal models

To verify the edibility in terms of safety and efficacy in the context of body weight control using the GuChE 10–1–7.5 hydrogels, animal experiments were conducted. It should be clarified that the edibility and oral safety measurement cannot be conclude from neither *in vitro* nor *in vivo* cytotoxicity test due to a totally different culture condition (neutral

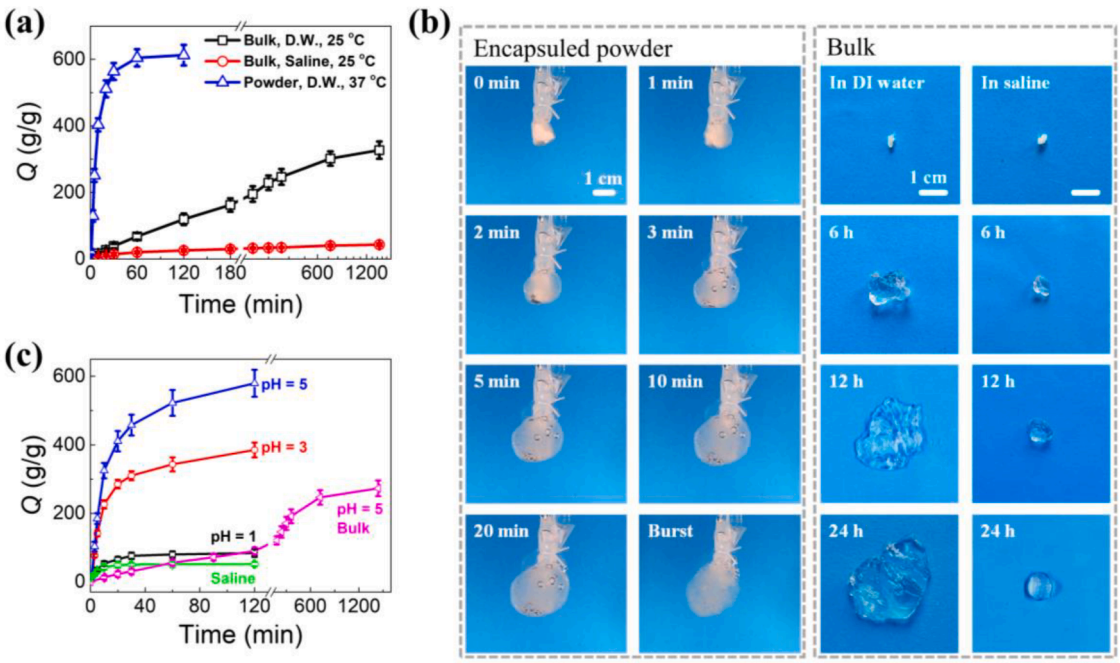

Fig. 3. Swelling kinetic of the GuChE hydrogel. (a, b) Time dependence of pH value and swelling ratio *Q* (25 °C) for the GuChE 10–1–7.5 (bulk) (a) and ChE 1–7.5 (b) sample (bulk). (c) Time dependence of swelling ratio *Q* (25 °C) in water and saline for the GuChE 10–1–7.5 sample (bulk). (d) Time dependence of swelling ratio *Q* (37 °C) in pH = 5 solution for the GuChE 10–1–7.5 sample (powder). (e) Adsorption process of GuChE 10–1–7.5 sample (powder) in pH = 5 solution (800 mL) stained by bromophenol red at 37 °C. The powder sample (about 0.2 g, marked by red dashed frame) was put in a non-swollen polypropylene net jacket and then immersed into the solution for 3 h.

condition for common cell experiment which acidic condition for oral safety test). Also, similar hydrogel is prepared in another reported works and is proved to be cytocompatible [38]. The animal experiment results are shown in Fig. 4. As the commercial capsules are too large to feed the rats and mice, liquid dispersant is employed in the experiments. For the safety of the edibility test, various doses of GuChE hydrogels were orally administrated with saline to the mice, namely, low dosage (L.D.) for 0.1 g/kg, medium dosage (M.D.) for 0.5 g/kg, high dosage (H.D.) for 1.0 g/kg, along with a control group without dosing. As shown in Fig. 4a, the mice with GuChE hydrogels show regular bodyweight increase, as do the ones in the control group. Herein, the saline is applied to suppress the swelling of the hydrogel (e.g., see Fig. 2b) and thus it is possible to dose the mice through the feeding needles. The GuChE powder was dispersed in a certain amount of saline to ensure its suction and injection using a feeding needle. The mixture was then fed to the mice. The experiment continued for a period of 28 days; 79 of 80 mice survived till the end of the experiment period during which they behaved normally without sluggishness, anorexia, emesis, or diarrhea. faeces of the rats were wetter which could be explained due to the indigestible hydrogel particles, though the detailed reason wasn't very clear. One male mouse in the M.D. group died at day 24, probably due to operational error. The mice experiment proved the oral safety of GuChE hydrogels.

To evaluate the efficacy of the bodyweight control, rats with higher bodyweight were selected and fed with GuChE hydrogels at the same dose levels. Here, the need is to have the edible hydrogel swell in the stomach but not in the oral cavity. Therefore, saline as a swelling suppression was not used; instead, dry GuChE was fed with pure PEG 400 as a dispersant, which aided in not suppressing its swelling when diluted with water. Thus, a certain amount of water was fed to the mice immediately after feeding the GuChE/PEG 400 mixture. Fig. 4b shows the weight gain for both male and female rats (see also Fig. S5), where all rats showed overall bodyweight increase (except the weight at day 0 because the weighing time and feeding method were different) and normal behavior. Though the bodyweight increases no matter the dose, the daily weight growth rate (WGR), i.e., the slope of the linear fitting of the weight gain vs. day curve, does show some apparent difference, which is seen in Fig. 4b and more clearly presented in Fig. 4c. The results show that all the WGR values of dosing groups are smaller than the control groups, which suggests the inhibition effect of GuChE hydrogels on bodyweight increase. Specifically, the medium dosing exerts the optimal inhibition effect, with WGR decreasing 25% for males (from 6.63 g/day to 4.89 g/day) and 18% for females (from 2.89 g/day to 2.16 g/day) as compared to the control group. Therefore, the inhibition effect on bodyweight increase of GuChE hydrogels is representative suggesting also its potential for bodyweight control capacity. As the drug dose for rats is commonly 5.2 times higher than a human dose, a potential dose of around 0.08 g/kg of GuChE for human adults would take optimum effect on bodyweight control.

Degradation of GuChE hydrogel under gastric fluid conditions should be considered, given that gastric fluid contains strong acid and digestion enzyme. Considering that the average stomach emptying time is about 2 to 4 h, we recorded the weight change of GuChE hydrogels in different solutions for a continuous 24 h period as an exaggerated test, and the results are shown in Fig. 4d. The weight of GuChE hydrogel decreases around 2% after immersing in PBS solution due to the ionized condition, and no degradation product is found in the eluent. While in pH = 1 and SGF (simulated gastric fluid) solutions, the weight of GuChE hydrogel decreases about 3% after 24 h due to acid hydrolysis; this is confirmed from the NMR result of the eluent, at where mainly contains *N*-acetyl-D-glucosamine (GlcNAc) as degradation products, as shown in Fig. S6. The weight change of GuChE hydrogel in SIF (simulated intestinal fluid) shows a 5% increase after 24 h without any degradation products detected, suggesting that a weak basic condition is favorable for hydrogel swelling and chemical stability. The degradation test demonstrated the enzyme stability of GuChE hydrogels and presented its potential to excrete with food through regular bowel movements.

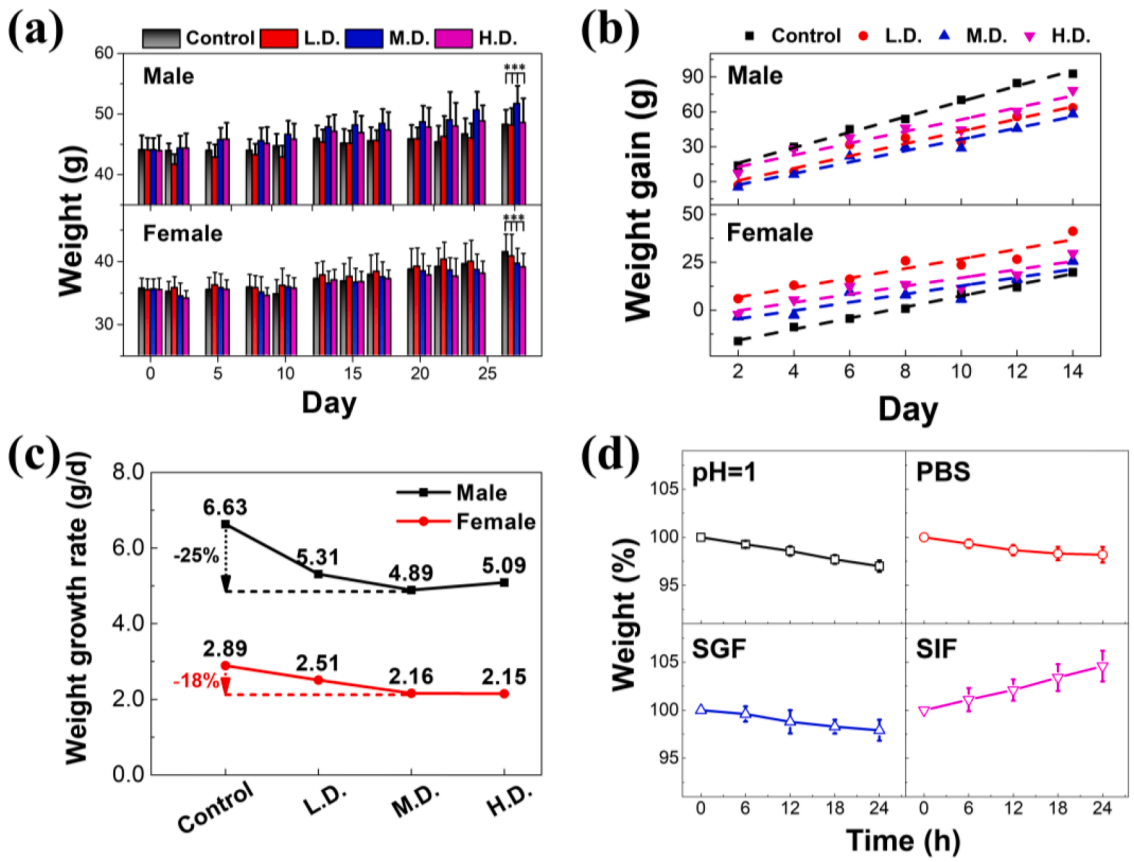

Fig. 4. Edibility and efficacy studies of the edible hydrogel using animal models. (a) Mice experiments to evaluate the safety of GuChE 10–1–7.5 hydrogels. Low dosage (L.*D.*): 0.1 g/kg; Medium dosage (*M.D.*): 0.5 g/kg; High dosage (*H.D.*): 1.0 g/kg. The significance level $***p < 0.001$, which was calculated by two-factor ANOVA without replication analysis. (b) Rat experiments to evaluate the bodyweight gain per day of GuChE 10–1–7.5 hydrogels. Low dosage (L.*D.*): 0.1 g/kg; Medium dosage (*M.D.*): 0.5 g/kg; High dosage (*H.D.*): 1.0 g/kg. (c) Weight growth rate (WGR, g/day) changes fitted from (b). (d) Degradation of GuChE 10–1–7.5 hydrogels in different solutions (37 °C).

2.4. Encapsuled edible hydrogels in a simulated and simplified digestive system

In the envisioned application, the GuChE hydrogel in the powder form is designed to be encapsuled in dissolvable gelatin capsule and then orally administrated with adequate water. Thus, the process of disintegration of the capsule in diluted SGF, followed by dispersion and swelling of the hydrogel should be considered under gastric motility. A simple simulated system was established to observe this process, as shown in Fig. 5. The system includes a single and replicate vertical

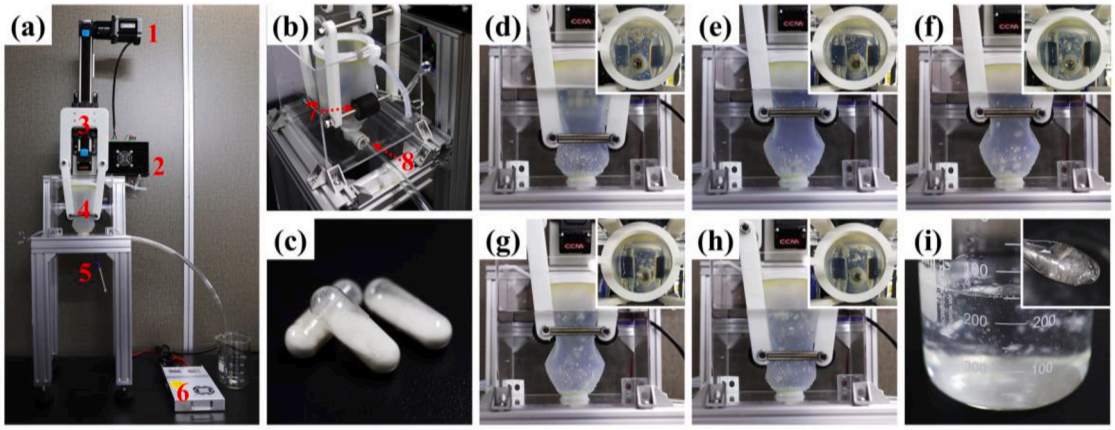

Fig. 5. Trial of the encapsuled edible hydrogels in simulated and simplified digestive system. (a, b) Front (a) and side view (b) of the simulated stomach system for the hydrogel excretion performance. Red numbers refer to each part of the system [1]: Motor system [2]; Motor speed controller [3]; Cantilever system for roller-squeezer [4]; Simulated stomach, which was made by PDMS and placed in a water bath [5]; Switch for the motor [6]; Power supplier [7]; Rubber roller, and the friction between it and PDMS was low [8]; A valve to simulate pylorus. (c) Photography of the gelatin capsules filled with 0.2 g/each of GuChE 10–1–7.5 powder sample (powder mesh was smaller than 50). (d–h) Front view of the chamber in water bath and the hydrogel/diluted SGF mixtures at different setpoint: (d) 0 min with 5 capsules; (e) 10 min after capsule disintegration; (f) 20 min; (g) 30 min; (h) 60 min. Insets were the top view of the chamber. (i) Hydrogel/diluted SGF mixtures after excretion from the simulated pylorus. Inset was the feature of the hydrogel particles.

motion with rollers squeezing on a PDMS-made stomach-like chamber, simulating simple gastric motility (Fig. 5a) and a valve with a similar tunnel size as the pylorus for hydrogel/diluted SGF mixture excretion, simulating the pylorus opening (Fig. 5b). The PDMS chamber is temperature-controlled by water bath at 37 °C, and the moving speed of the rollers is set as 4 mm/s (about 3.5 cycles per minute), which is similar to the normal gastric motility of healthy human adults [39,40]. At the initial state, the chamber contains 30 mL SGF (pH = 1.5), which is similar to healthy human adults after having fasted for one night [41]. Five gelatin capsules filling 0.2 g/each (Fig. 5c) with 300 mL water are poured into the chamber (Fig. 5d); then the rollers begin to move and apply pressure to the chamber (Movie S4). After 10 mins, the gelatin capsules disintegrate and release the GuChE hydrogels into the diluted SGF solution (Fig. 5e). The GuChE hydrogels gradually disperse in the solution and swell with time, which then endows the solution with some viscosity to make the hydrogel particles float in the central chamber, as seen in Fig. 5f to 5h. Because of the fast swelling of hydrogels in powder form, some hydrogel particles form aggregated clusters, requiring longer time motility to disintegrate, and as a result, after 1 hour, some hydrogel particles continue to float in the solution before excretion (Fig. 5h and i). The motility process continues for 1 hour then moves to the excretion process, which can be accomplished by opening the valve (Movie S5), where the hydrogel mixture can be observed from the excretion tube. It is admitted that the present simplified system only simulates a mild gastric motion and constant pH value, which cannot fully reproduce the actual gastrointestinal environment. On the other hand, the actual gastric shearing is in fact much stronger than the present system, which would lead to a more evenly dispersion of the hydrogel and may present a better swelling behavior in the stomach. The modulus of the hydrogel mixture is measured by a rheometer and shows about 40 Pa at $\omega = 0.3$ rad/s (Fig. S7), which is close to the swollen hydrogel with a swelling ratio of 300, which is also similar to the modulus of yogurt. It should be noted that the retention time of the hydrogel mixture and excretion differs individually, but the simulation process presents a friendly usage of GuChE hydrogel, which can provide satiety and avoid foreign body sensations that often happen when using intragastric balloons.

3. Discussion

This paper describes a method to synthesize a natural polymer-based hydrogel with good shrinkage tolerance in acids, based on three main components, namely ethylene glycol diglycidyl ether (EGDE), guanidine hydrochloride monohydrate (GuHCl·H_2O), and chitin molecules. The GuChE hydrogel presents high swelling ratios both in DI water (i.e., 300 for bulk and 600 for powder) and in acids (i.e., 50 for bulk and 80 for powder), along with fast swelling properties (i.e., reaching 80% of the maximum swelling ratio in just 20 min for powder hydrogels). Through animal experiments, oral safety and ability for weight control were demonstrated. Several aspects can be considered to further improve the performance of this hydrogel. One is to improve the reaction efficiency. The chemical reaction between EGDE and GuHCl·H_2O, which is mainly the reaction between the epoxy and guanidine groups, always competes with the self-condensation of EGDE, resulting in atactic and random polymerization. Additionally, alkaline hydrolysis of guanidine that generates ammonia also decreases the ratio of the major reaction. Grafting ratio is calculated as 0.244 according to the NMR spectra result (Fig. S1a), suggesting many side reactions. To improve the reaction efficiency, one solution can be the employment of an effective catalyzer, while controlling the alkali concentration to decrease the side reaction described above. Another area of improvement could be the double-edged sword effect led by the significant hydrophilicity of the GuChE hydrogel. On the one hand, this significant hydrophilicity endows the high swelling ratio, but it also tends to agglomerate among hydrogel particles, leading to inhomogeneous swelling and suppression of the swelling performance in practical scenario, especially in the encapsuled form. Soluble dispersants could be a candidate to enhance the swelling homogeneity in future studies. In summary, we believe that the present work of using natural polymers to develop edible, shrinkage tolerance in acids, high swelling ratio, and fast swelling hydrogels would find many unprecedented healthcare applications in the gastrointestinal tract.

4. Materials and methods

4.1. Materials

The chitin was extracted from a squid pen (purchased from Golden-Shell Biochemical Co. Ltd, Zhejiang, China) through following procedures. The squid pen was deproteinized by 1 mol/L sodium hydroxide (NaOH) and demineralized by 1 mol/L hydrochloric acid (HCl) solution. Each step was repeated two to three times to remove all proteins, minerals, lipids, and ashes in the squid pen. The pretreated squid pen was then washed with adequate DI water, freeze-dried, and subsequently kept in a desiccator before use. The M_η of the purified chitin powder was determined to be 1.0×10^7 to 1.4×10^7 g/mol in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) by static light scattering measurement (Brookhaven BI-200SM, U.S.A.) at 20 °C. The degree of acetylation of purified chitin is measured as 93.6% according to the element analysis result (Table. S2). Residual ash in purified chitin is determined to be ~ 1.0% by element analysis. Ethylene glycol diglycidyl ether (epoxy ≈ 0.7) (EGDE) was purchased from Adamas Reagent, Ltd. (China). Guanidine hydrochloride monohydrate (GuHCl·H_2O) and other necessary chemicals were analytical-grade and purchased from Shanghai Chemical Reagent Co. Ltd. (China) and used as received. Commercial food applied in this work were boiled skinless chicken breast, boiled broccoli, boiled egg, Oreo cookies, KFC potato paste with meat sauce, fresh ripe banana, and Greek yogurt.

4.2. Preparation of chitin solutions

The purified chitin was dispersed into an aqueous 20 *wt.*% KOH/4 *wt.*% urea solution to obtain 1 *wt.*% chitin suspension. Subsequently, the suspension was cooled under −25 °C overnight and then stirred for 2 h at room temperature. The cooling-stirring process was repeated twice to achieve a viscose and homogenous chitin solution. After dissolution, the chitin solution was frozen under −25 °C before the preparation of hydrogels.

4.3. Synthesis of superabsorbent hydrogels

The frozen chitin solution was first thawed at room temperature. After the ice was softened, moderate stirring was applied, with simultaneously dosing of GuHCl·H_2O and EGDE in desired amounts. The stirring continued for about 2 h until the solution temperature reached room temperature. The resultant mixture was then transferred to a petri dish and placed on an orbital shaker at 35 °C for crosslinking reaction. After 3 h, a very soft hydrogel was formed. The hydrogel was then immersed into a 20% (v/v) isopropanol (IPA) solution and stored overnight to stop the reaction completely. Subsequently, the adequate 50% (v/v) IPA solution was applied several times to make the hydrogel shrink, while eliminating KOH, urea, and unreacted chemicals. After thoroughly washing using an IPA solution, the hydrogel was cut into 1 × 1 cm^2 pieces and dried at 35 °C with ventilation to obtain bulk forms; it was then stored in a desiccator before further measurements. The dry sample was coded as GuChE X-Y-Z, as shown in Table S1, where X, Y, and Z refers to the initial dose of GuHCl·H_2O (g/100 g solution), chitin (g/100 g solution), and EGDE (mL/100 g solution), respectively. To obtain a powder sample, the dry bulk sample was ground into 50 mesh powder using a high-power grinder (IKA A10 Basic Mill, Germany). To identify the function of GuHCl·H_2O in the hydrogel, chitin-EGDE hydrogel was also prepared for comparation. Within the chitin concentration applied here, chitin solution could not form gel by neither heating nor adding GuHCl·H_2O only.

4.4. Swelling ratio test at different fluids

For the bulk sample, a small piece of dry sample (about 0.1 g) was immersed in 200 mL DI water (pH = 6.8–7.2), NaCl solution (0–0.20 mol/L) or buffer solution (pH = 1–7) for 24 h at room temperature (25 °C). Before weighing, the excess fluid on the surface of the hydrogel was removed using filter papers. The swelling ratio Q was calculated by:

$$Q = \frac{m_w - m_0}{m_0} \tag{1}$$

where m_w and m_0 were the mass of wetted sample and dry sample.

For powder samples, a certain amount of sample (about 0.1 g) was placed in a polyethylene/polypropylene tea bag (about 0.3–0.4 g) and then immersed into 200 mL DI water (pH = 6.8–7.2) at 25 °C. The total mass of wetted sample and tea bag was measured after 24 h. Before weighing, the excess fluid was removed using filter papers until no water could be squeezed from the tea bag. The swelling ratio Q was calculated by:

$$Q = \frac{m_w - m_t - m_0}{m_0} \tag{2}$$

where m_w, m_t, and m_0 were the mass of wetted sample, tea bag, and dry sample, respectively.

4.5. Characterization of swelling equilibrium curve

For the bulk sample, a small piece of dry sample (bulk, about 0.1 g) was immersed in 200 mL DI water (pH = 6.8–7.2), pH = 5 solution and saline at room temperature. The swelling ratio Q was measured at different time set-points. At each set-point, the time counting paused, and the sample was quickly taken out; the surface fluid was then removed using filter paper. After the sample was weighed, it was put back into the water or solution and the time counting was continued. The swelling ratio Q was calculated by:

$$Q = \frac{m_T - m_0}{m_0} \tag{3}$$

where m_T and m_0 were the mass of wetted sample at each time set-point and the mass of dry sample, respectively. Without further description, the time counting and weighing method was the same as described here. During the swelling test in pH = 5 solution, the pH value of the solution at each set-point was also recorded to build the pH variation curve.

For the powder sample, a certain amount of sample (about 0.1 g) was placed in a polyethylene/polypropylene tea bag (about 0.3–0.4 g) then immersed into 200 mL DI water (pH = 6.8–7.2), NaCl solution (0–0.20 mol/L) or buffer solution (pH = 1–7) at 37 °C. The total mass of wetted sample and tea bag was measured at different time set-points. Before weighing, the excess fluid was removed using filter papers until no water could be squeezed from the tea bag. The swelling ratio Q was calculated by:

$$Q = \frac{m_{total} - m_t - m_0}{m_0} \tag{4}$$

where m_{total}, m_t and m_0 were the mass of wetted sample at each time set-point, the mass of tea bag and dry sample, respectively.

4.6. Degradation test of powder sample in different solutions

A certain amount of powder sample (about 0.1 g) was placed in a polyethylene/polypropylene tea bag (about 0.3–0.4 g), which was then immersed into 200 mL acidic solution (pH = 1), PBS solution (pH = 6.8), simulated gastric fluid (SGF, pH = 1.5) and simulated intestinal fluid (SIF, pH = 7.4) at 37 °C, respectively. The total mass of wetted sample and tea bag was measured at different time set-points. Before weighing, the excess fluid was removed using filter papers until no water could be squeezed from the tea bag. According to previous experiments, the equilibrium swelling was achieved after 24 h. Hence the residual weight ratio (Q_R) was calculated by:

$$Q_R = \frac{m_T}{m_{24}} \times 100\% \tag{5}$$

where m_T and m_{24} were the mass of wetted sample at each time set-point and at 24 h, respectively. The degraded chemical from acidic solution (pH = 1) was further characterized using liquid NMR. Before measurement, the eluent was neutralized by 0.1 mol/L NaOH solution and desalted through recrystallization. The purified eluent was mixed with 10% (v/v) deuterium oxide after which the NMR measurement was applied.

4.7. Rheological analysis

The mechanical properties of the hydrogel and chewed food paste were measured with the Ares-G2 rheometer (TA Instruments, U.S.A.) under oscillatory shear. The hydrogel and food paste sample with a thickness of 0.3 mm was sandwiched between parallel rheometer plates with a Peltier device for temperature control. The temperature was set to 37 °C, and the evaporation was minimized by coating silicon oil around the edge of the plate and sample. The shear storage moduli (G') as function of frequency (ω) was measured by setting the strain amplitude as 10%, which was within a linear viscoelastic regime.

4.8. Element analysis

Quantitative analysis of carbon, hydrogen, nitrogen, and oxygen in chitin and GuChE sample was carried out on a commercial element analyzer (Elementar, Germany). The degree of deacetylation (*D.D.*) of chitin was calculated from the element analysis result [42]:

$$D.D.(\%) = \left(1 - \frac{C/N - 5.145}{6.816 - 5.145}\right) \times 100 \tag{6}$$

where C/N was the ratio of carbon and nitrogen content.

4.9. Chemical structure analysis

Liquid-state nuclear magnetic resonance (NMR) spectra of the reactants and eluents were recorded using a Bruker BioSpin 600 MHz with a cryo-probe at ambient temperature. Deuterium oxide (D 99.8%, TCI) and d_6-DMSO (D 99.9% with 0.05% TMS, Cambridge Isotope Laboratories, Inc.) were used as solvent. The concentration of solute was set as 5% in weight ratio. For the characterization of GuChE hydrogel, a certain amount of dry powder sample and deuterium oxide were successively put into the NMR tube to allow high swelling of the sample. Excessive deuterium oxide was removed from the tube before measurement. Solid-state ^{13}C NMR spectra of chitin and GuChE sample were recorded using a Bruker BioSpin 500 MHz spectrometer with a cross-polarization/magic angle spinning (CP-MAS) probe at ambient temperature. Fourier transform infrared spectroscopy (FTIR) result was recorded with a Nicolet iS50 spectrometer (Thermo Fisher Scientific Inc.) using attenuated total reflectance (ATR) mode.

4.10. Crystal structure analysis

The X-ray diffraction (XRD) patterns of chitin and the GuChE sample were recorded on a Bruker powder X-ray diffractometer (D8 Advance) operated at 40 kV and 40 mA in reflection mode with Cu $K\alpha$ radiation (λ = 1.542 Å), a scanning speed of 9 °C/min and a step-size of 0.019 over the 2θ range from 5° to 60° All samples were ground into fine particles to eliminate the effects of the crystalline orientation. The relative crystal index (*CrI*) was used to determine the crystallinity of single peak and all crystalline peaks, which was calculated from the ratio of the area of

crystalline peaks to the total area [43].

4.11. Mechanical compression test

The water bondability of GuChE hydrogel was carried out by mechanical compression on a universal testing system (Instron 6800 series, U.S.A.) under constant strain. The strain was fixed at 50% and 80% for hydrogel snapshots. The stress was removed after the hydrogel was fractured at the strain of 80%. The composition of the GuChE hydrogel was 5:1.0:5, which was tough enough to stand and retain its shape. The hydrogel was cut into a $3 \times 3 \times 2$ cm^3 piece in a pyramid shape and the surface water was removed with filter papers before compression.

4.12. Mice experiment for oral safety evaluation

Forty male and 40 female Chinese Kunming (KM) mice were purchased at approximately 10 weeks of age. They were housed individually in small cages and provided with a standard diet at standard ambient temperature and humidity. The weight of male and female KM mice was 44 g and 35 g, respectively, on average as they came. First, the safety of the GuChE sample was evaluated for which the mice were grouped and fed with the powder sample at a dosage of 0.1 g/kg (low dosage), 0.5 g/kg (medium dosage), and 1.0 g/kg (high dosage) through a feeding needle. To suppress the fast and high swelling of the powder GuChE sample, the GuChE samples were mixed with saline for sample dispersion and feeding. The sample feeding was conducted at 8:00 ~ 10:00 every day before an ad libitum diet and continued for 28 days. The weight at day 0 was measured before sample dosing, after which the weight of each rat was recorded every 2 days at 16:00 ~ 18:00. All mice were sacrificed using CO_2 after experiments. The procedures were approved by the Animal Care and Use Committee. (Approval number: IACUC-20,210,913–16)

4.13. Rats experiment for weight-control evaluation

Twenty-five male and 25 female Sprague-Dawley (SD) rats were purchased at approximately 10 weeks of age and housed in groups in cages provided. The rats were provided with a standard diet at standard ambient temperatures and humidity. The male and female SD rats were fed with a regular diet of 350 g and 200 g, respectively, on average before the test. To evaluate the weight-control capacity of the GuChE sample, each rat was fed with the powder sample in a dosage of 0.1 g/kg (low dosage), 0.5 g/kg (medium dosage), and 1.0 g/kg (high dosage) through a feeding needle. To suppress the swelling of the powder GuChE sample, it was mixed with PEG400 for dispersion and feeding. Right after feeding the GuChE/PEG400 mixture, water (1 mL/100 g bodyweight) was fed to the rats. For the PEG groups, each rat was fed with 3 mL of 10 wt.% PEG400 solution. Every day, the sample feeding took place at 8:00–10:00; the rats then waited for 2 h before the ad libitum diet, after which the rats fasted starting at 17:00 (drinking water was still provided). The experiment continued for 14 days. The weight at day 0 was measured before sample dosing and after that, the weight of each rat was recorded every 2 days in the afternoon before fasting. All rats were sacrificed using CO_2 after experiments. The procedures were approved by the Animal Care and Use Committee. (Approval number: IACUC-20,220,221–30) The daily weight growth rate (WGR) was calculated by linear fitting of the weight-day curve from day 2 to day 14. Data of day 0 was not included into the fitting due to the different weighing set-point and feeding method.

Data and materials availability

All data are available in the main text or the supplementary materials.

CRediT authorship contribution statement

Junchao Huang: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Zhuang Zhang:** Software, Visualization. **Hanqing Jiang:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.apmt.2023.101786.

References

[1] A.T. Eggebrecht, S.L. Ferradal, A. Robichaux-Viehoever, M.S. Hassanpour, H. Dehghani, A.Z. Snyder, T. Hershey, J.P. Culver, Mapping distributed brain function and networks with diffuse optical tomography, Nat. Photonics 8 (2014) 448–454.
[2] J.A. Rogers, T. Someya, Y.G. Huang, Materials and mechanics for stretchable electronics, Science 327 (2010) 1603–1607.
[3] D.J. Lipomi, M. Vosgueritchian, B.C.K. Tee, S.L. Hellstrom, J.A. Lee, C.H. Fox, Z. N. Bao, Skin-like pressure and strain sensors based on transparent elastic films of carbon nanotubes, Nat. Nanotechnol. 6 (2011) 788–792.
[4] M. Kaltenbrunner, T. Sekitani, J. Reeder, T. Yokota, K. Kuribara, T. Tokuhara, M. Drack, R. Schwodiauer, I. Graz, S. Bauer-Gogonea, S. Bauer, T. Someya, An ultra-lightweight design for imperceptible plastic electronics, Nature 499 (2013) 458–463.
[5] W. Gao, C. Yu, Wearable and Implantable Devices for Healthcare, Adv. Healthc. Mater. 10 (2021), 2101548.
[6] Q. Yang, T. Wei, R.T. Yin, M. Wu, Y. Xu, J. Koo, Y.S. Choi, Z. Xie, S.W. Chen, I. Kandela, S. Yao, Y. Deng, R. Avila, T.L. Liu, W. Bai, Y. Yang, M. Han, Q. Zhang, C. R. Haney, K. Benjamin Lee, K. Aras, T. Wang, M.H. Seo, H. Luan, S.M. Lee, A. Brikha, N. Ghoreishi-Haack, L. Tran, I. Stepien, F. Aird, E.A. Waters, X. Yu, A. Banks, G.D. Trachiotis, J.M. Torkelson, Y. Huang, Y. Kozorovitskiy, I.R. Efimov, J.A. Rogers, Photocurable bioresorbable adhesives as functional interfaces between flexible bioelectronic devices and soft biological tissues, Nat. Mater. 20 (2021) 1559–1570.
[7] Z. Zou, C. Zhu, Y. Li, X. Lei, W. Zhang, J. Xiao, Rehealable, fully recyclable, and malleable electronic skin enabled by dynamic covalent thermoset nanocomposite, Sci. Adv. 4 (2018) eaaq0508.
[8] Z.H. Lin, W.S. Hsu, A. Preet, L.H. Yeh, Y.H. Chen, Y.P. Pao, S.F. Lin, S. Lee, J.C. Fan, L. Wang, Y.P. Chiu, B.S. Yip, T.E. Lin, Ingestible polysaccharide battery coupled with a self-charging nanogenerator for controllable disinfection system, Nano Energy 79 (2021), 105440.
[9] A. Abramson, D. Dellal, Y.L. Kong, J. Zhou, Y. Gao, J. Collins, S. Tamang, J. Wainer, R. McManus, A. Hayward, M.R. Frederiksen, J.J. Water, B. Jensen, N. Roxhed, R. Langer, G. Traverso, Ingestible transiently anchoring electronics for microstimulation and conductive signaling, Sci. Adv. 6 (2020) eaaz0127.
[10] X. Liu, C. Steiger, S. Lin, G.A. Parada, J. Liu, H.F. Chan, H. Yuk, N.V. Phan, J. Collins, S. Tamang, G. Traverso, X. Zhao, Ingestible hydrogel device, Nat. Commun. 10 (2019) 493.

[11] X. Wang, W. Xu, P. Chatterjee, C. Lv, J. Popovich, Z. Song, L. Dai, M.Y.S. Kalani, S. E. Haydel, H. Jiang, Food-Materials-Based Edible Supercapacitors, Adv. Mater. Technol. 1 (2016), 1600059.

[12] M. Mimee, P. Nadeau, A. Hayward, S. Carim, S. Flanagan, L. Jerger, J. Collins, S. McDonnell, R. Swartwout, R.J. Citorik, V. Bulovic, R. Langer, G. Traverso, A. P. Chandrakasan, T.K. Lu, An ingestible bacterial-electronic system to monitor gastrointestinal health, Science 360 (2018) 915–918.

[13] R. Wang, L. Zhou, W.X. Wang, X.M. Li, F. Zhang, *In vivo* gastrointestinal drug-release monitoring through second near-infrared window fluorescent bioimaging with orally delivered microcarriers, Nat. Commun. 8 (2017).

[14] P.C. Zhao, X.F. Xia, X.Y. Xu, K.K.C. Leung, A. Rai, Y.R. Deng, B.G. Yang, H.S. Lai, X. Peng, P. Shi, H.L. Zhang, P.W.Y. Chiu, L.M. Bian, Nanoparticle-assembled bioadhesive coacervate coating with prolonged gastrointestinal retention for inflammatory bowel disease therapy, Nat. Commun. 12 (2021).

[15] X. Jin, C. Wei, C. Wu, W. Zhang, Gastric fluid-induced double network hydrogel with high swelling ratio and long-term mechanical stability, Compos. Part B Eng. 236 (2022), 109816.

[16] G. Mun, I. Suleimenov, K. Park, H. Omidian, in Biomedical Applications of Hydrogels Handbook, R.M. Ottenbrite, K. Park, T. Okano, Eds. Springer (New York, New York, NY), (2010), pp. 375–391.

[17] S. Ayazi, J.M. Leers, A. Oezcelik, E. Abate, C.G. Peyre, J.A. Hagen, S.R. DeMeester, F. Banki, J.C. Lipham, T.R. DeMeester, P.F. Crookes, Measurement of gastric pH in ambulatory esophageal pH monitoring, Surg. Endosc. 23 (2009) 1968–1973.

[18] G.K. Elyashevich, N.G. Bel'nikevich, S.A. Vesnebolotskaya, Swelling-contraction of sodium polyacrylate hydrogels in media with various pH values, Polym. Sci. Ser. A 51 (2009) 550–553.

[19] M. Madaghiele, C. Demitri, I. Surano, A. Silvestri, M. Vitale, E. Panteca, Y. Zohar, M. Rescigno, A. Sannino, Biomimetic cellulose-based superabsorbent hydrogels for treating obesity, Sci. Rep. 11 (2021) 21394.

[20] L.J. Aronne, J.E. Anderson, A. Sannino, E. Chiquette, Recent advances in therapies utilizing superabsorbent hydrogel technology for weight management: a review, Obes. Sci. Pract. 8 (2021) 1–8.

[21] L. Dong, H.J. Wichers, C. Govers, Chitin Chitosan (2019) 145–167.

[22] J. Zheng, G. Cheng, Q. Li, S. Jiao, C. Feng, X. Zhao, H. Yin, Y. Du, H. Liu, Chitin oligosaccharide modulates gut microbiota and attenuates high-fat-diet-induced metabolic syndrome in mice, Mar. Drugs (2018), https://doi.org/10.3390/md16020066.

[23] C.S. Kong, J.A. Kim, S.S. Bak, H.G. Byun, S.K. Kim, Anti-obesity effect of carboxymethyl chitin by AMPK and aquaporin-7 pathways in 3T3-L1 adipocytes, J. Nutr. Biochem. 22 (2011) 276–281.

[24] B. Xu, M.I. Jacobs, O. Kostko, M. Ahmed, Guanidinium group remains protonated in a strongly basic arginine solution, Chemphyschem 18 (2017) 1503–1506.

[25] X. Qu, A. Wirsen, A.C. Albertsson, Novel pH-sensitive chitosan hydrogels: swelling behavior and states of water, Polymer 41 (2000) 4589–4598 (Guildf).

[26] J. Ostrowska-Czubenko, M. Gierszewska, M Pierog, pH-responsive hydrogel membranes based on modified chitosan: water transport and kinetics of swelling, J. Polym. Res. 22 (2015) 153.

[27] X.P. Shen, J.L. Shamshina, P. Berton, G. Gurau, R.D. Rogers, Hydrogels based on cellulose and chitin: fabrication, properties, and applications, Green Chem. 18 (2016) 53–75.

[28] M. Yoshino, M. Shibata, T. Ikeda, Y. Namba, The EFFECT of pH of alkaline solution on epichlorohydrin hydrolysis: studies on the derivatives of epichlorohydrin. III, J. Jpn. Oil Chem. Soc. 14 (1965) 182–185.

[29] F.V. Drozdov, V.M. Kotov, Guanidine: a simple molecule with great potential: from catalysts to biocides and molecular glues, INEOS Open 3 (2020) 200–213.

[30] Y.F. Pan, X. Zhao, X.N. Li, P.X. Cai, Green-based antimicrobial hydrogels prepared from bagasse cellulose as 3D-scaffolds for wound dressing, Polymers 11 (2019) 1846. Basel.

[31] Y. Guan, L. Qian, H. Xiao, A. Zheng, Preparation of novel antimicrobial-modified starch and its adsorption on cellulose fibers: part I. Optimization of synthetic conditions and antimicrobial activities, Cellulose 15 (2008) 609–618.

[32] F. Horkay, P.J. Basser, Ionic and pH effects on the osmotic properties and structure of polyelectrolyte gels, J. Polym. Sci. Part B Polym. Phys. 46 (2008) 2803–2810.

[33] J. Landsgesell, D. Beyer, P. Hebbeker, P. Košovan, C. Holm, The pH-dependent swelling of weak polyelectrolyte hydrogels modeled at different levels of resolution, Macromolecules 55 (2022) 3176–3188.

[34] M.R.C. Marques, R. Loebenberg, M. Almukainzi, Simulated biological fluids with possible application in dissolution testing, Dissolut. Technol. 18 (2011) 15–28.

[35] J.F. Cao, W. Xu, Y.Y. Zhang, Y. Shu, J.H. Wang, A salt stimulus-responsive nanohydrogel for controlled fishing low-density lipoprotein with superior adsorption capacity, ACS Appl. Mater. Interfaces 13 (2021) 4583–4592.

[36] S.W. Xiao, X.M. He, Z.Q. Zhao, G.B. Huang, Z.Z. Yan, Z.C. He, Z.P. Zhao, F. Chen, J. T. Yang, Strong anti-polyelectrolyte zwitterionic hydrogels with superior self-recovery, tunable surface friction, conductivity, and antifreezing properties, Eur. Polym. J. 148 (2021), 110350.

[37] Y. Zhang, K.Y. Zhao, Z.J. Zhang, H.K. Xie, Z.Y. Li, Z. Lin, C. Mo, W.D. Yang, X. L. Wang, J.F. Wei, Polypropylene non-woven supported calcium alginate hydrogel filtration membrane for efficient separation of dye/salt at low salt concentration, Desalination 500 (2021), 114845.

[38] J. Huang, M. Frauenlob, Y. Shibata, L. Wang, T. Nakajima, T. Nonoyama, M. Tsuda, S. Tanaka, T. Kurokawa, J.P. Gong, Chitin-based double-network hydrogel as potential superficial soft-tissue-repairing materials, Biomacromolecules 21 (2020) 4220–4230.

[39] H. Kozu, I. Kobayashi, M.A. Neves, M. Nakajima, K. Uemura, S. Sato, S. Ichikawa, PIV and CFD studies on analyzing intragastric flow phenomena induced by peristalsis using a human gastric flow simulator, Food Funct. 5 (2014) 1839–1847.

[40] Y. Li, L. Fortner, F. Kong, Development of a gastric simulation Model (GSM) incorporating gastric geometry and peristalsis for food digestion study, Food Res. Int. 125 (2019), 108598.

[41] D.M. Mudie, K. Murray, C.L. Hoad, S.E. Pritchard, M.C. Garnett, G.L. Amidon, P. A. Gowland, R.C. Spiller, G.E. Amidon, L. Marciani, Quantification of gastrointestinal liquid volumes and distribution following a 240ml dose of water in the fasted state, Mol. Pharm. 11 (2014) 3039–3047.

[42] M.R. Kasaai, J. Arul, C. Charlet, Intrinsic viscosity-molecular weight relationship for chitosan, J. Polym. Sci. Polym. Phys. 38 (2000) 2591–2598.

[43] S. Park, J.O. Baker, M.E. Himmel, P.A. Parilla, D.K. Johnson, Cellulose crystallinity index: measurement techniques and their impact on interpreting cellulase performance, Biotechnol. Biofuels 3 (2010) 10.

[44] M.C. Peng, V. Sethu, A. Selvarajoo, Performance study of chia seeds, chia flour and Mimosa pudica hydrogel as polysaccharide-based superabsorbent polymers for sanitary napkins, Mater. Today Commun. 26 (2021), 101712.

[45] J. Irfan, M.A. Hussain, M.T. Haseeb, A. Ali, M. Farid-ul-Haq, T. Tabassum, S. Z. Hussain, I. Hussain, M. Naeem-ul-Hassan, A pH-sensitive, stimuli-responsive, superabsorbent, smart hydrogel from psyllium (Plantago ovata) for intelligent drug delivery, RSC Adv. 11 (2021) 19755–19767.

[46] M.T. Huseeb, M.A. Hussain, S.H. Yuk, S. Bashir, M. Nauman, Polysaccharides based superabsorbent hydrogel from Linseed: dynamic swelling, stimuli responsive on-off switching and drug release, Carbohydr. Polym. 136 (2016) 750–756.

[47] M.U. Ashraf, M.A. Hussain, G. Muhammad, M.T. Haseeb, S. Bashir, S.Z. Hussain, I. Hussain, A superporous and superabsorbent glucuronoxylan hydrogel from quince (Cydonia oblanga): stimuli responsive swelling, on-off switching and drug release, Int. J. Biol. Macromol. 95 (2017) 138–144.

[48] R.R. Mallepally, I. Bernard, M.A. Marin, K.R. Ward, M.A. McHugh, Superabsorbent alginate aerogels, J. Supercrit. Fluids 79 (2013) 202–208.

[49] R. Meena, K. Prasad, A.K. Siddhanta, Development of a stable hydrogel network based on agar-kappa-carrageenan blend cross-linked with genipin, Food Hydrocoll 23 (2009) 497–509.

[50] A.W. Chan, R.A. Whitney, R.J. Neufeld, Semisynthesis of a Controlled Stimuli-Responsive Alginate Hydrogel, Biomacromolecules 10 (2009) 609–616.

[51] F. Naeem, S. Khan, A. Jalil, N.M. Ranjha, A. Riaz, M.S. Haider, S. Sarwar, F. Saher, S. Afzal, pH responsive cross-linked polymeric matrices based on natural polymers: effect of process variables on swelling characterization and drug delivery properties, Bioimpacts 7 (2017) 177–192.

[52] B.X. Cheng, B.Y. Pei, Z.K. Wang, Q.L. Hu, Advances in chitosan-based superabsorbent hydrogels, RSC Adv. 7 (2017) 42036–42046.

[53] D. Jeong, S.W. Joo, Y. Hu, V.V. Shinde, E. Cho, S. Jung, Carboxymethyl cellulose-based superabsorbent hydrogels containing carboxymehtyl beta-cyclodextrin for enhanced mechanical strength and effective drug delivery, Eur. Polym. J. 105 (2018) 17–25.

[54] M.A. Hussain, L. Kiran, M.T. Haseeb, I. Hussain, S.Z. Hussain, Citric acid crosslinking of mucilage from Cydonia oblonga engenders a superabsorbent, pH-sensitive and biocompatible polysaccharide offering on-off swelling and zero-order drug release, J. Polym. Res. 27 (2020) 49.

[55] X.J. Lv, W.C. Zhang, Y.E. Liu, Y. Zhao, J.S. Zhang, M.X. Hou, Hygroscopicity modulation of hydrogels based on carboxymethyl chitosan/alginate polyelectrolyte complexes and its application as pH-sensitive delivery system, Carbohydr. Polym. 198 (2018) 86–93.

[56] A. Pourjavadi, S. Barzegar, G.R. Mahdavinia, MBA-crosslinked Na-Alg/CMC as a smart full-polysaccharide superabsorbent hydrogels, Carbohydr. Polym. 66 (2006) 386–395.

[57] T. Fekete, J. Borsa, E. Takacs, L. Wojnarovits, Synthesis of carboxymethylcellulose/starch superabsorbent hydrogels by gamma-irradiation, Chem. Cent. J. 11 (2017) 46.

[58] H. Tang, H. Chen, B. Duan, A. Lu, L. Zhang, Swelling behaviors of superabsorbent chitin/carboxymethylcellulose hydrogels, J. Mater. Sci. 49 (2014) 2235–2242.