Supplementary Information

Core-shell hydrogel with synergistic super absorption and long-term acid resistance stability: a novel gastric retention drug delivery carrier

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Preparation of Simulated Gastric Fluid

Simulated Gastric Fluid (SGF) is a liquid that simulates the environment of gastric fluid and is often used in simulated digestion experiments in vitro. According to the Chinese Pharmacopoeia, the preparation method is as follows: dilute hydrochloric acid 16.4 mL (equivalent to hydrochloric acid 3.84 mL), add water about 800 mL and pepsin 10 g, shake well, add water to dilute into 1000 mL.

Encapsulation of orlistat with CS-HM @ CMCNa

Firstly, 0.5 g orlistat was slowly added to 100 mL 0.1 mol / L HCl and dissolved at 40℃, and then 3.0 g CS and 1.0 g HM powder were slowly added into the solution[1]. After mechanical stirring

for a certain period of time, CS-HM/gel solution was formed, which was squeezed into 1 mol/L NaOH at a speed of 0.15 mm/s with a syringe to form beads, all of which were extruded and solidified for a certain period of time, and washed to neutrality. Then put it into 0.1wt % CMCNa to wrap, and then washed with deionized water once, and then added to 5wt % EDC solution for crosslinking, washed with deionized water twice, and finally freeze-dried.

The degree of group formation in the gel precursor solution

Tab. S1 Comparison of the peak areas of C = O and N-H and glycosidic bonds in the gel precursor solution at different stirring times

Name	Glycoside Bond Peak Area	C=O Peak Area	C=O Ratio	N-H Peak Area	N-H Ratio
CS-HM/gel solution$_{1h}$	0.229	2.684	11.72	1.950	8.52
CS-HM/gel solution$_{2h}$	0.429	5.305	12.37	3.737	8.71
CS-HM/gel solution$_{3h}$	0.349	4.394	12.59	3.368	9.65
CS-HM/gel solution$_{4h}$	0.163	1.996	12.25	1.607	9.86
CS-HM/gel solution$_{5h}$	0.331	4.712	14.24	3.652	11.03
CS-HM/gel solution$_{6h}$	0.093	1.506	16.19	1.044	11.23
CS-HM/gel solution$_{7h}$	0.323	5.266	16.30	3.637	11.25
CS-HM/gel solution$_{8h}$	0.282	4.608	16.34	3.172	11.25

The semi-quantitative analysis (Tab. S1) of the C = O and N-H of the amide bond in the gel precursor solution at different stirring times was carried out. It was found that the ratio of the group peak area of the gel precursor solution reached the maximum value in the reaction process when the stirring time was 6h, that is, the strongest time of the group interaction, and the ratio did not change significantly after continuing to extend the time. Combined with the problem of industrial production time, the gel precursor solution with stirring for 6h was selected for subsequent preparation.

The morphology and size of CS-HM and CS-HM@CMCNa

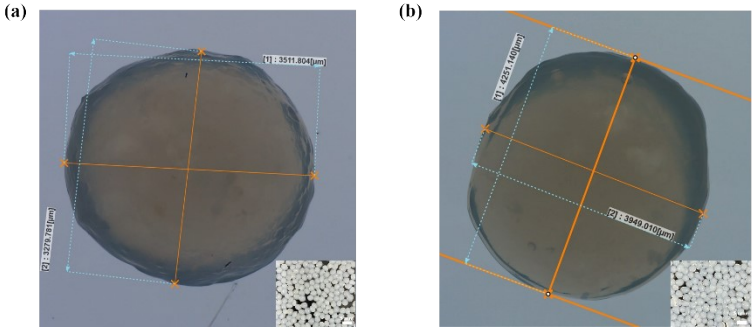


Figure. S1 (a) The morphology and size of CS-HM; (b) the morphology and size of CS-HM@CMCNa.

Due to the limited process conditions, the syringe extrusion method is currently used to try to make the gel spherical. We are also constantly optimizing the process in subsequent studies to make the shape more perfect. Under the optical microscope, the diameter of CS-HM is about 3.40 mm, and the diameter of CS-HM@CMCNa is about 4.10 mm. After constructing an outer polymer network in CMCNa solution, the size of the gel beads becomes larger.

The swelling of CS-HM@CMCNa in different pH environments

Tab. S2 The swelling kinetic parameters of CS-HM@CMCNa after soaking in different pH environments

Name	Q_{eq} (g/g)	Q_{∞} (g/g)	1/A (g/g·s)
CS-HM@CMCNa/pH=1.2	95.7	99.5	27.9
CS-HM@CMCNa/ pH=5	40.2	41.2	10.3
CS-HM@CMCNa/ pH=7	39.4	38.7	33.5
CS-HM@CMCNa/ pH=12.8	21.9	19.6	4.0

The curves of the reciprocal of the absorption rate and the swelling time were fitted from the swelling data obtained in four different external environments[2, 3]. The Q_{∞} of the four external environments was calculated, which was basically consistent with the Qt of the swelling equilibrium. It is proved that the swelling of CS-HM@CMCNa in different external environments follows the second-order swelling kinetic equation. The swelling degree of CS-HM@CMCNa soaked in pH=1.2 is the largest, and the initial absorption rate represented by 1/A is also the largest, which proves that the reversible dynamic bond is continuously generated in the strong acidic environment, the absorption sites are increased, and the absorption capacity is still improved.

The properties of CS-HM@CMCNa after long-term swelling in different pH environments

Tab. S3 The properties of CS-HM@CMCNa after swelling in different pH for 13 h.

Environment	M (g)	M_t (g)	Dispersion Behavior	Final State
pH=1.2	10.47	10.36	Dispersion	Complete spherical shape
pH=5.0	4.92	5.00	Dispersion	Complete spherical shape
pH=7.0	4.84	4.76	Dispersion	Complete spherical shape
pH=12.8	3.10	2.86	Dispersion	Complete spherical shape

There was no significant difference between the M_t of CS-HM@CMCNa after soaking in different pH environments for 13 hours and the M at swelling equilibrium, which indicates that CS-HM@CMCNa can maintain long-term stability across various pH conditions. This stability is attributed to the core-shell design, which ensures that CS-HM@CMCNa remains stable in different pH environments, preserving its appearance and overall dispersion.

Mechanical properties analysis of CS-HM@CMCNa

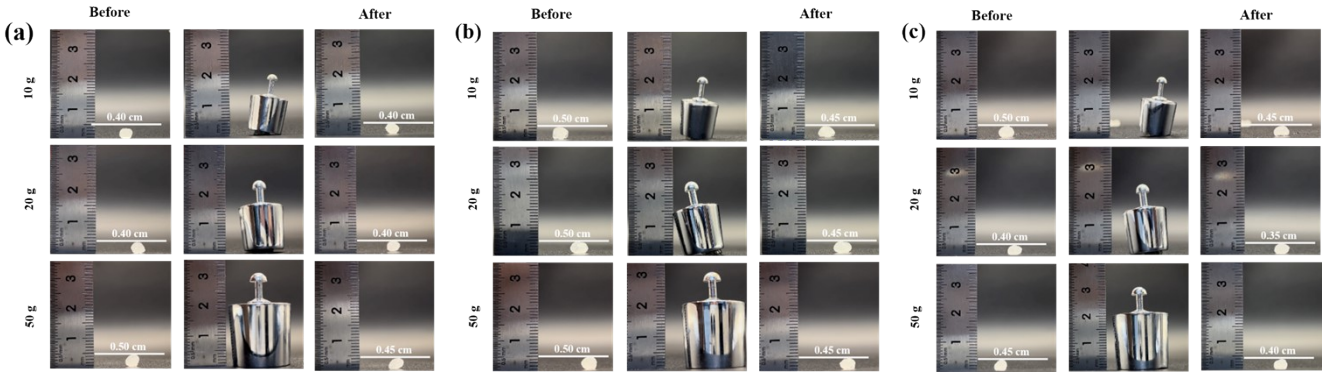
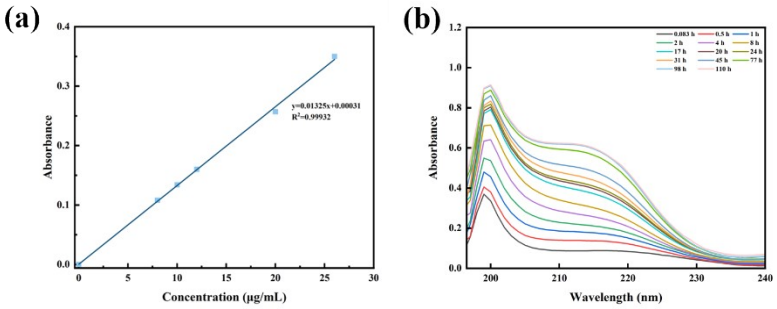


Figure. S2 CS-HM@CMCNa was immersed in SGF for different time and then compressed by external compression: (a) swelling equilibrium time; (b) 3 days; (c) 6 days.

The maximum intragastric pressure of solid food was 53.60 ± 8.40 mmHg[4], which was about 7146.0 Pa (1 mmHg = 133.32 Pa). According to the pressure formula, F ≈ 0.03 ~ 0.04 N ≈ 3.1 ~ 4.1 g. Therefore, 10 g, 20 g and 50 g weights were used to apply pressure on CS-HM@CMCNa in acid swelling equilibrium, 3 days and 6 days (the end point of release when the drug was loaded). It can be observed that when the pressure is much higher than that in the stomach, the deformation is small, and the height is only reduced by 11 % at most. After compression, the gel beads are not broken, the shape remains intact, and have excellent compression resistance.



Drug release data supplement

Figure. S3 (a) Standard curve from UV-vis spectrum of orlistat; (b) the UV release curves of Orl-CS-HM@CMCNa at different time.

The UV absorption peak of orlistat is located at 195 nm, and the absorption peak of orlistat in Orl-CS-HM@CMCNa is about 200 nm. The red shift from 195 nm to 200 nm proves that the drug group interacts with the ions of the polysaccharide, which proves that CS-HM@CMCNa is not a simple adsorption drug, which can ensure the stable release of the drug in the gastric acid

environment.

Tab. S4 Statistical data of cumulative drug release.

Time (h)	$M_{Release}$ (mg)	Cumulative Release Percentage (%)
0.08	27.82	31.6
0.50	30.54	34.7
1.00	36.20	41.2
2.00	41.41	47.1
4.00	48.35	55.0
8.00	53.86	61.3
17.00	59.67	67.9
20.00	60.66	69.0
24.00	61.71	70.2
31.00	62.92	71.6
45.00	64.88	73.8
77.00	67.00	76.2
98.00	68.66	78.1
110.00	68.99	78.4

According to the Formula (2-6), the final mass of the drug loaded in CS-HM@CMCNa was 87.9 mg. According to the Formula (2-7), the cumulative release mass at different times can be obtained, and the cumulative release percentage can be obtained.

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3. Y. Zhou, S. Fu, S. Yang and H. Zhan, *Transaction of China Pulp and Paper*, 2012, **27**, 40-44.
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