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Amino Acid-Based Hydrogels with Dual Responsiveness for Oral Drug Delivery

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Article Type Communication

Amino Acid-Based Hydrogels with Dual Responsiveness for Oral Drug Delivery [a]

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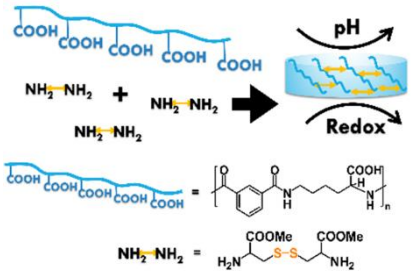
This study reports a series of novel amino acid-based dual-responsive hydrogels. Prepared by a facile one-pot EDC coupling reaction, the solid content, structure and mechanical behavior of hydrogels could be easily adjusted by changing the concentrations of the polymers and the crosslinkers. With pH-responsive anionic pseudo-peptides as backbones and disulfide-containing L-cystine dimethyl ester as crosslinkers, these hydrogels are able to collapse and form relatively compact structure at an acidic pH, while swelled and partly dissociated at a neutral pH. Further addition of DTT facilitated complete degradation of hydrogels. The high loading efficiency, rapid but complete triggered-release and good biocompatibility make these hydrogels promising candidates for oral delivery.

FIGURE FOR ToC_ABSTRACT

[a] **Supporting Information** is available online from the Wiley Online Library.
[b] These authors contributed equally to this work.


COOH
pH
Redox
Redox
COOMe
S-S

1. Introduction

Oral delivery is the most convenient and common means of drug administration. Being the primary administration route, oral drug delivery provides many advantages, including low cost, ease of use and high patient compliance compared to injection.[1,2] Yet there are also significant barriers in gastrointestinal (GI) tract that may lead to insufficient drug delivery, such as the highly acidic physiological environment in the stomach and enzymatic disruption in the small intestine. Hence, delivery vehicles that protect drug payloads from the harsh GI environment are highly expected. Among them, the hydrogel is one of the commonly used.[3,4]

Hydrogels are three-dimensional water-swollen polymer networks.[5] They usually contain a high amount of water but retain their structure owing to chemical and/or physical crosslinks. Because of these structural similarities to the excellular matrix, hydrogels are considered as biocompatible, thus having great prospects in biomedical applications.[6,7] Stimuli-responsive hydrogels, among others, are of special interest.[8,9] These hydrogels have the ability to swell, shrink or degrade corresponding to environmental stimuli, such as pH, redox potential, temperature and enzymatic activity. For oral delivery, pH-responsive hydrogels which are composed of pH-responsive polymers, have been intensively investigated, due to significant pH variations in GI tract. At low pH (around 1-3 in stomach[10]), hydrogels shrink and form compact structures to minimize drug leakage; at higher pH (around 6-7.5 in the small intestine[10]) these hydrogels swell to release payloads. Protein payloads, such as insulin, could be delivered to intestine via this strategy.[11–13] Despite the substantial advantages of pH-responsive hydrogels, the payload release is relatively slow and incomplete.

Hydrogels with dual-responsiveness provide a promising approach for oral delivery with better controlled and more efficient release behavior at target sites.[14,15] It has been reported that hydrogels with pH-sensitive swelling and enzymatic degradation could facilitate colon-

specific delivery.[14] Herein, we propose the design of a novel pH- and redox-responsive hydrogel synthesized from poly(L-lysine isophthalamide) (PLP) crosslinked with L-cystine dimethyl ester dihydrochloride (CDE). PLP is a biocompatible, lysine-based, metabolically derived pseudo-peptide which has a pKa of 4.4.[16,17] The pseudo-peptidic polymer is easy-to-synthesize and each structural unit contains one pendant carboxylic acid group available for pH-responsive functionalities and further modifications. Its constituent components, lysine and isophthalic acid, have low toxicity and do not accumulate in the body, and it has been previously employed to prepare hydrogel systems with pH-triggered controlled release of model drugs over a wide size range (0.3-2000 kDa).[18] In this paper, PLP was crosslinked by CDE, an amino acid derivative bearing a disulfide bond. The redox potential decreases along the gastrointestinal tract from −67 ± 90 mV in the proximal small bowel to −196 ± 97 mV in the distal small bowel and then to −415 ± 72 mV in the right colon, a level much lower than the standard reduction potential for disulfide bonds (about −250 mV).[19] The reductive cleavage of disulfide bonds has been demonstrated to specifically occur in colon, leading to the degradation of disulfide-crosslinked networks and complete release of payloads.[20,21] The hydrogels with different solid contents were crosslinked by an EDC coupling reaction. Infrared spectra and elemental analyses were used to confirm gel structures. Swelling behavior, scanning electron microscope (SEM) morphology and dynamic rheology were examined to evaluate dual-responsive properties of the hydrogels. Model drug loading efficiencies and release profiles in response to pH and redox stimuli were investigated and the desired controlled-release behavior was identified. Finally, the cytotoxicity of the hydrogels was also evaluated to demonstrate their biocompatibility.

2. Results and Discussion

2.1. Synthesis and characterization of hydrogels

As demonstrated in **Figure 1a**, hydrogels were prepared by EDC coupling of PLP and CDE at room temperature in a glass vial with a diameter of 12 mm (experimental details are available in the Supporting Information). Different polymer concentrations were employed, resulting in the hydrogels with different solid contents. **Table 1** gives various hydrogel formulae used in this study. For all hydrogels, the molar ratio of crosslinkers and polymer residuals was kept constant according to previous optimization.[18] As the polymer concentration decreased from 10.0 wt% to 2.5 wt%, the solid contents of hydrogels decreased from 7.5 wt% to 4.3 wt%. When the polymer concentration further decreased below 2.5 wt%, hydrogels were not readily formed even after overnight treatment. This ascribes to the fact that a low solid content delayed gel formation.

X-ray photoelectron spectroscopy (XPS) was carried out to confirm the presence of sulfur in hydrogels. As shown in **Figure 1b**, there were three main peaks at approximately 532, 400 and 285 eV, corresponding to oxygen (O 1s), nitrogen (N 1s) and carbon (C 1s) elements respectively. The small peak at approximately 164 eV was assigned to sulfur (S 2p). After fitting the signal with the S $2p_{3/2}$ and S $2p_{1/2}$ spin orbit coupling contributions, the observed binding energy for the S $2p_{3/2}$ contribution was observed at 163.7 eV (**Figure 1c**). This binding energy is characteristic of disulfide compounds,[21] which indicates polymers were successfully crosslinked by CDE. Furthermore, the crosslinking ratio could be deduced from the atomic composition of polymer backbones and disulfide-bond containing crosslinkers (see **Table 1**). The crosslinking degree of Gel 1 was the highest due to the more efficient crosslinking reaction at the higher polymer concentration while the other three gels had similar crosslinking degrees.

Infra-red (IR) spectra were also used to characterize the molecular structures of hydrogels. To investigate the protonation of polymer backbones at different pH values, hydrogels were

soaked in different pH buffers overnight followed by lyophilization before IR study. In **Figure 1d**, the characteristic peaks of hydrogels were located at 3300 cm^{-1} (w, ν_s O–H of carboxylic acid groups), 2930 cm^{-1} and 2865 cm^{-1}(s, ν_s C–H), 1730 cm^{-1}(s, ν_s C=O of carboxylic acid groups), 1634 cm^{-1}(s, Amide I), 1527 cm^{-1}(s, Amide II), 1438 cm^{-1}(s, δ C–H), 1270 cm^{-1}(w, Amide III). Noticeably, the band intensity centered at around 1730 cm^{-1} increased to a great extent as pH declined.[23,24] This evidence revealed the increment of protonated carboxylic acid, as hydrogels became protonated at lower pH. However, at pH 7.4, the bands corresponding to COO^- at approximately 1590 cm^{-1} could not be clearly identified, due to overlaps with amide bands.

2.2. pH-responsive swelling behavior

The pH-responsiveness of hydrogels was investigated by swelling studies. **Figure 1e** shows the swelling ratio q which can be calculated as the equilibrium weight of hydrogels in different buffers divided by their weight after lyophilization. As expected, q increased as pH increased for all hydrogels. When the carboxylic acid groups presented in the hydrogel network were deprotonated, the electrostatic repulsion enabled hydrogels to swell, and vice versa.[11] With the decrease in solid contents, the swelling ratios increased at both pH conditions studied. This can be attributed to the lower density of the hydrogel network which holds more water. Among all, Gel 2 had the largest variation of swelling ratio (Δq) from pH 3.0 to pH 7.4 at about 5 while $\Delta q<3$ for all other hydrogels. This indicates that the combination of a lower crosslinking degree and higher solid contents probably made hydrogels more competent in pH-responsive swelling.

SEM images revealed the pH-responsive porous structures of hydrogels. Before SEM, hydrogels were equilibrated in three buffers at pH 7.4, 5.0 and 3.0 responsively, followed by lyophilization. **Figure 2** shows that the pore sizes of Gel 1 at different pHs varied significantly. At pH 3.0, Gel 1 shrank and accordingly formed relatively compact but porous

structures. The pore sizes were around 1 μm in diameter (**Figure 2a**). By comparison, at pH 7.4, the hydrogel became swollen and pore sizes increased by almost 100 times (**Figure 2c**). At pH 5.0, polymer backbones in Gel 1 were probably partially protonated, leading to a wide range of pore sizes, from several to one hundred microns (**Figure 2b**). The other hydrogels were also highly porous and showed similar pH-responsive pore size variations (data not shown), but their pore sizes were very different (see **Figure 3**). The differences in pore size could be attributed to different solid contents and crosslinking degrees.[25] Gel 1 was highly crosslinked with the highest polymer network density, thus bearing the smallest pores. However, Gel 3 and Gel 4 with the largest pores (50-200 μm) appeared more delicate and fragile. Small pieces of gels were observed in **Figures 3c** and **3d**, indicating that the hydrogel networks may have collapsed and even broken during lyophilization and SEM processing probably due to the low modulus. These results were consistent with the swelling behavior of the hydrogels at different pHs. Gel 3 and Gel 4 with larger pores had relatively higher swelling ratios, due to less resistance to water transport within the gels.

Mechanical properties of hydrogels under different conditions were studied by dynamic rheological measurements. All gels were equilibrated in different buffers for 48 h before measurements. In **Figure 4a**, the storage modulus (*G'*) and the loss modulus (*G''*) of Gel 2 at pH 3.0, pH 7.4, and pH 7.4 with DTT were plotted as a function of strain. At pH 3.0, elasticity dominated ($G' \sim 24$ kPa > $G'' \sim 7$ kPa) over the entire frequency range studied and both *G'* and *G''* were independent of frequency, indicating that the gel was at a quasi-solid state. However, both the increase of pH and the addition of DTT induced substantial changes in hydrogel structure. At pH 7.4, the gel behaved viscoelastic at low frequency (loss tangent, $\tan\delta \approx 0.9$) and *G'* (~ 400 Pa) was significantly lower than the *G'* at pH 3.0. Moreover, both modules showed a strong dependency on frequency and *G''* surpassed *G'* when frequency increased to 14 rad s^{-1}, indicating that Gel 2 was more at a quasi-liquid state.[26] The

significant variations of the mechanical behavior resulted from the interactions of polymer networks within the hydrogels. At acidic pH, the pendent carboxylic acid groups of the PLP polymer were protonated, thus forming compact domains by hydrogen bonding and hydrophobic interactions. When pH increased, carboxylic acid groups were deprotonated and thus negatively charged. The electrostatic repulsion of these groups remarkably expanded the gel networks, leading to partial gel dissociation. Similarly, with the addition of DTT at pH 7.4, *G''* surpassed *G'* at a higher frequency, so the hydrogel was more liquid-like. Though *G'* was almost independent of frequency, the value was even lower, with only 1% of the *G'* at pH 3.0. This could be ascribed to the reduction of disulfide bonds in the hydrogel by DTT, thus making the hydrogel dissociate thoroughly.

Figure 4b compares the storage modulus of different hydrogels at pH 3.0 and 7.4 when oscillatory shear stress was applied at 1 rad s^{-1}. As expected, all gels had a significantly higher *G'* in an acidic environment due to the pH-induced protonation of polymer pendent groups. Gel 1 had the largest *G'* at both pH 3.0 and 7.4 (115 kPa and 1.3 kPa respectively), while Gel 4 had the lowest *G'* (only 2 kPa and 46 Pa respectively). The noticeable differences in *G'* suggest that storage modulus was strongly dependent on the solid contents and crosslinking degrees.[27,28] Because Gel 4 was too fragile to handle at high pH, it was excluded from the drug loading and release study.

2.3. In vitro model drug loading and release

The drug loading and in vitro release study was conducted using fluorescein as a model drug. The pH-responsive swelling properties were utilized to load drugs actively. Specifically, hydrogels were immersed in the fluorescein solution in the swollen state and then collapsed by addition of the concentrated hydrochloride acid solution. In this way, the model drugs loaded could be retained within hydrogels with high efficiency. **Figure 5a** shows the weight incorporation (the weight of loaded model drug divided by the total weight of the loaded gel

after lyophilization) and loading efficiency (the amount of loaded model drug divided by the total amount of model drug in the loading solution) of fluorescein in different hydrogels. The weight percentage of model drug in those hydrogels ranged from 40.3% to 64.8%. Gel 3 had the largest weight incorporation owing to its larger pore sizes and less compressed polymeric network. The loading efficiency ranged from 44.7% to 55.9%. Gel 2 had a slightly higher loading efficiency than the other two hydrogels, possibly due to its largest variation of swelling ratio (**Figure 1e**). After loading of model drugs, the hydrogels were immersed in different buffers to release drugs at pH 3.0, 5.0 and 7.4 responsively. These three conditions were chosen as they represent the pH gradients in GI tract – the highest pH in the stomach, the pH in the duodenum and in ileum respectively.[10] In **Figure 5b**, it is shown that after 24 h of incubation in a shaking water bath at 37 oC, only less than 5% of drugs were released at pH 3.0 and less than 10% at pH 5.0. By contrast, around 90% were released at pH 7.4 for all hydrogels. The results indicate that these hydrogels could successfully retain drugs at gastric acid but release them at intestinal pH within 24 h.

Then a kinetics study was carried out to monitor the drug release process. As shown in **Figure 5c**, drug release at pH 3.0 and 5.0 both remained very low throughout the period studied (less than 5% and 10%, respectively). At pH 7.4, the percentage of released model drugs increased almost linearly to 71% during the first 5 h, presenting a near zero-order release pattern. This might be attributed to the swelling of hydrogels, widely reported in pH-responsive ionic hydrogels, such as poly(acrylic acid) hydrogels,[29,30] and poly(N,N-dimethylacrylamide) hydrogels. [31] By contrast, when DTT was induced as a redox trigger, the release became degradation-controlled. Within the first 3 h, more than 80% of drugs were released, also in a near zero-order release pattern, and then a nearly complete release could be achieved after 5 h. This suggests that the addition of DTT led to an absolute dissociation of the hydrogel, thus leading to a more rapid and complete release within a short period.

2.4. In vitro cytotoxicity of hydrogels

Though all components of these hydrogels were reported as biocompatible,[18] the AlamarBlue assay was carried out to evaluate hydrogels' cytotoxicity, by measuring the variations of the metabolic activity of Hela cells treated with different gel concentrations. As shown in **Figure 5d**, the viabilities of the cells were all higher than 90% at the gel concentration up to 5 mg mL^{-1}, indicating that all those hydrogels had negligible cytotoxicity.

3. Conclusions

In summary, an attempt was made to develop smart and efficient hydrogel drug carriers. To this end, novel pH- and redox-responsive, amino-acid based hydrogels were synthesized from poly(L-lysine isophthalamide) (PLP) crosslinked with L-cystine dimethyl ester dihydrochloride (CDE). The solid content, structure and mechanical behavior of hydrogels could be easily adjusted by changing the concentrations of the polymers and the crosslinkers. It has been shown that at an acidic pH, the hydrogels collapsed and formed relatively compact structure, while at a neutral pH, the hydrogels swelled and partly dissociated. Further addition of DTT facilitated complete degradation of hydrogels. With high loading efficiency, rapid but complete triggered-release at specific sites and good biocompatibility, these hydrogels could be potential carriers for oral drug delivery.

Supporting Information

Supporting Information is available from the Wiley Online Library.

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Keywords: hydrogel, pH-responsive, redox-responsive, oral delivery

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Table 1. The formulae of hydrogels with different solid contents

No.	PLP (mg)	CDE (mg)	EDC (mg)	NHS (mg)	Polymer concentration (wt%)	Solid content (wt%) [a)]	Crosslinking ratio (mol%) [b)]
Gel 1	100	25	139	21	10.0	7.5	15.8
Gel 2	75	19	104	17	7.5	6.0	13.0
Gel 3	50	13	70	10	5.0	5.3	13.4
Gel 4	25	6	35	5	2.5	4.3	13.6

a) Defined as the weight of a hydrogel disk after lyophilization divided by its weight before lyophilization (see Equation 1 in the Supporting Information).
b) Defined as the molar ratio of crosslinkers to PLP residuals, which was calculated according to the XPS results (see Table S1 in the Supporting Information).

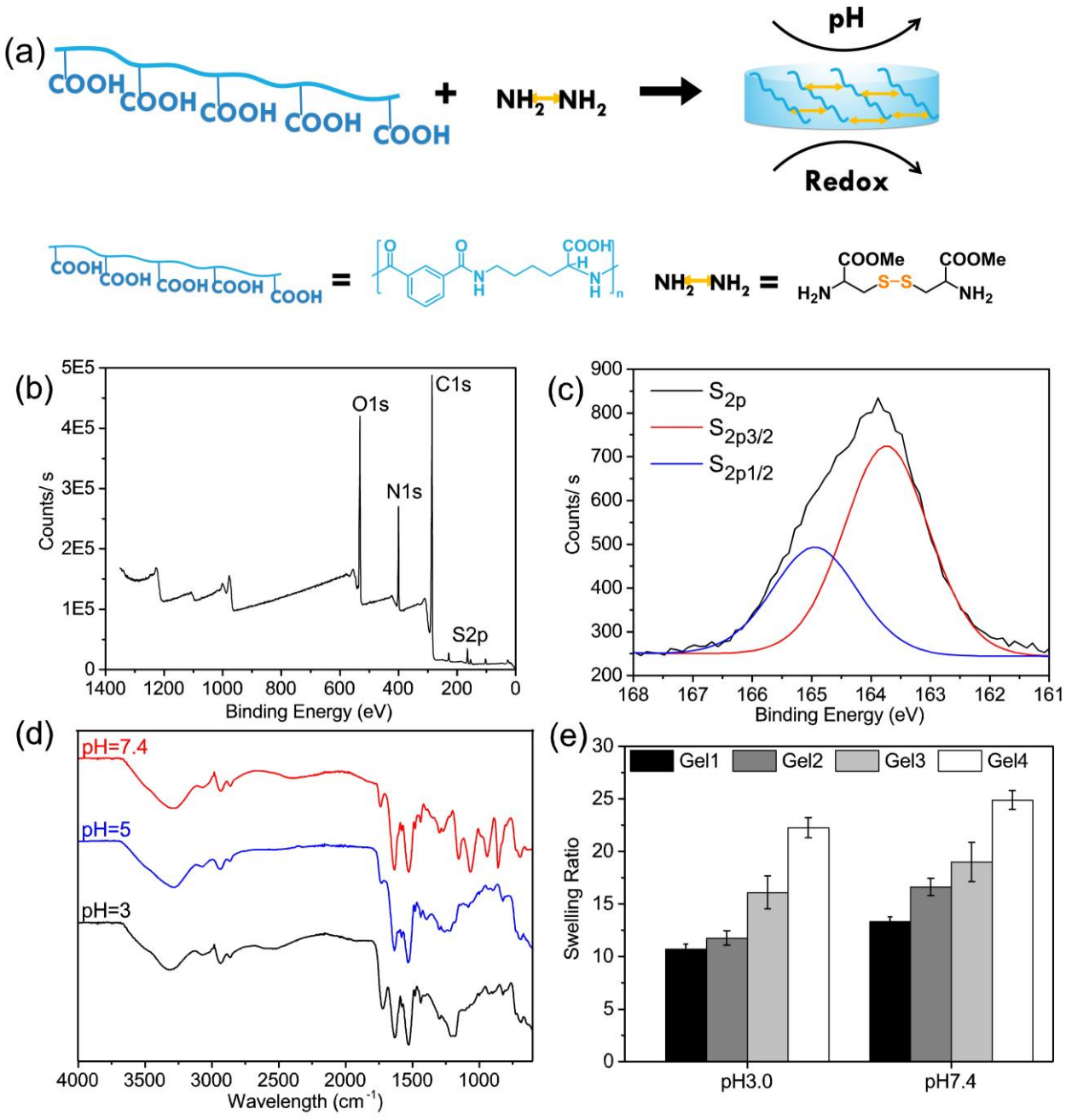

Figure 1. (a) Schematic representation of dual-responsive hydrogels; (b) The survey XPS spectrum of Gel 2; (c) the S 2p high resolution spectrum of Gel 2; (d) the FTIR spectra of Gel 2 at pH 3.0 (black), 5.0 (blue) and 7.4 (red) respectively; (e) swelling ratios of different hydrogels at pH 3.0 and 7.4. The swelling ratio *q* is defined as the weight of hydrogel in specific buffer divided by the weight after lyophilization (n=3).

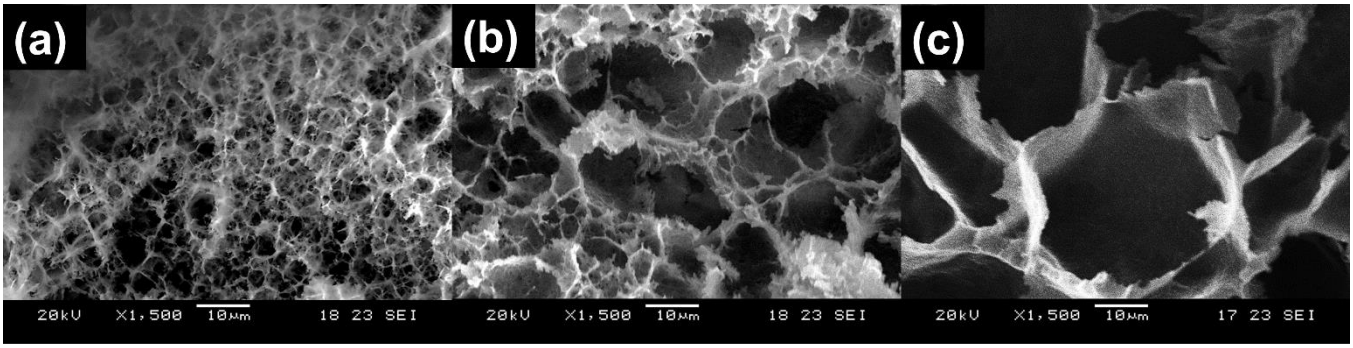

Figure 2. SEM images of Gel 1 (a) at pH 3.0; (b) pH 5.0 and (c) pH 7.4. The scale bar represents 10 μm.

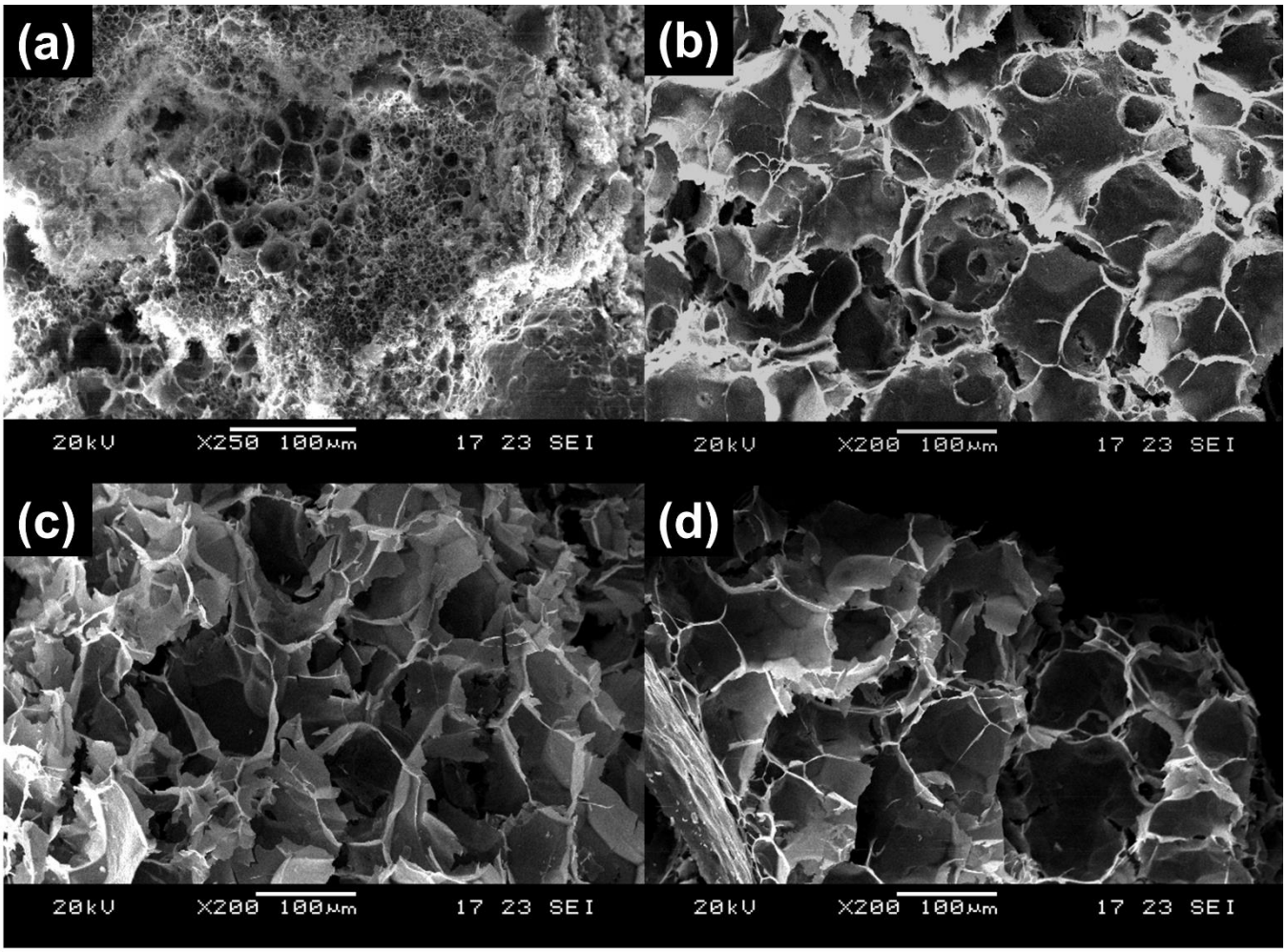

Figure 3. SEM images of different Gels at pH 5.0: (a) Gel 1; (b) Gel 2; (c) Gel 3 and (d) Gel 4. The scale bar represents 100 μm.

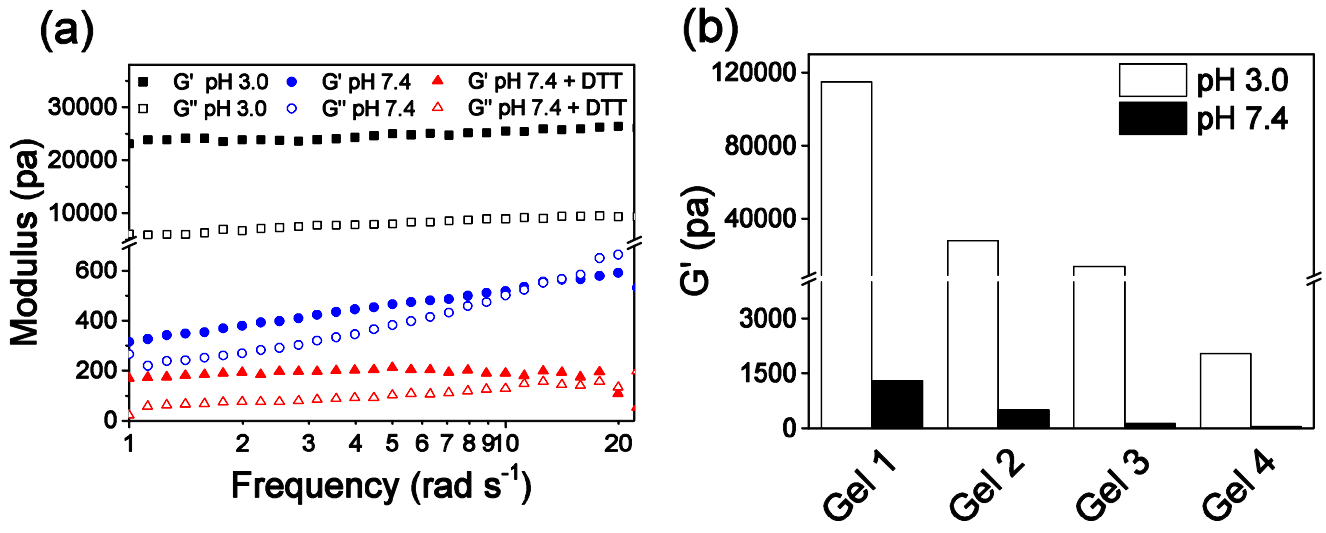

Figure 4. Rheology analyses of the Gels at different pHs. (a) Storage modulus G' and loss modulus G'' of Gel 2 versus frequency at pH 3.0, pH 7.4, and pH 7.4 with DTT. (b) Comparison of storage modulus G' of four hydrogels at pH 3.0 and 7.4. Oscillatory shear stress was applied at 1 rad s^{-1}.

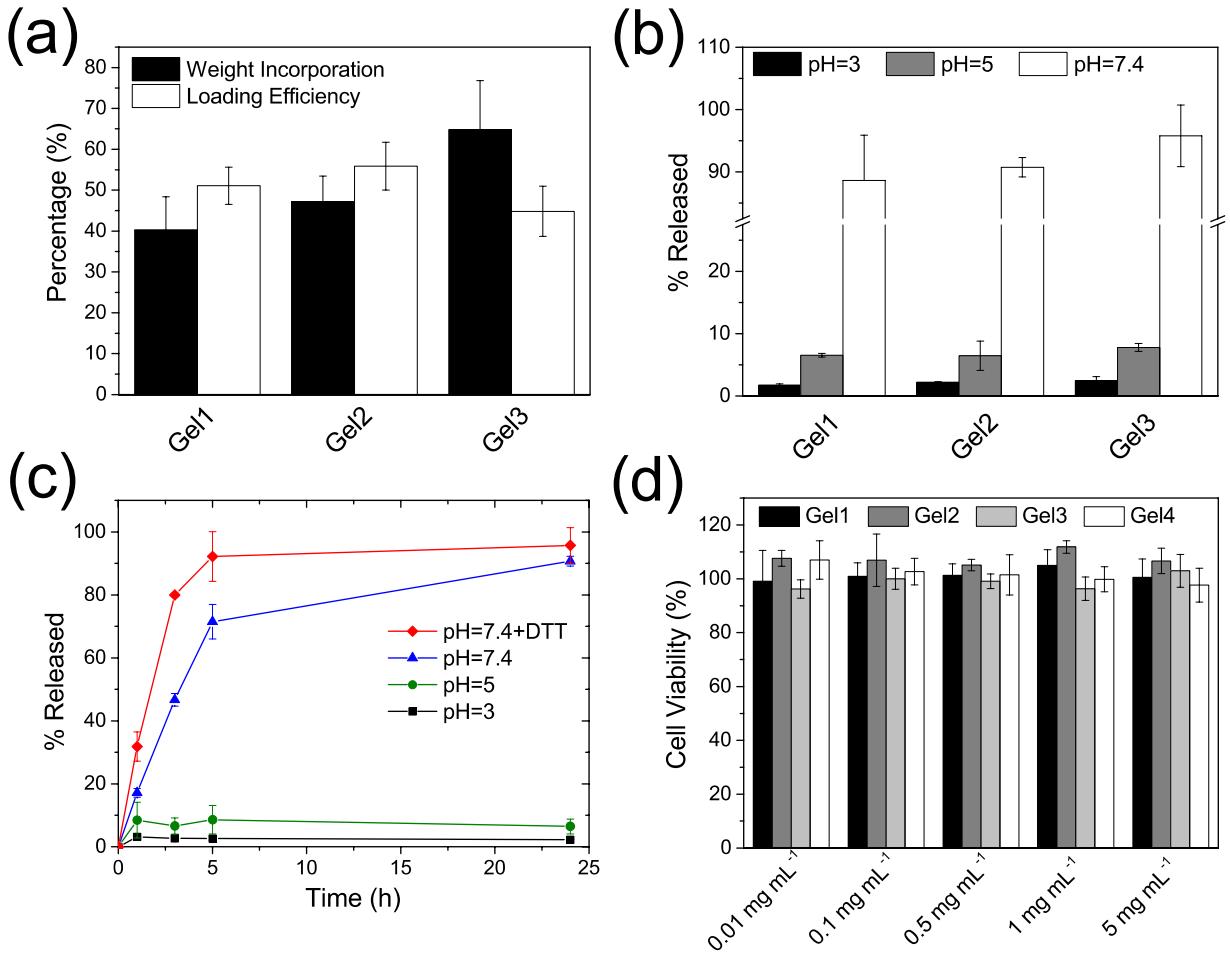

Figure 5. (a) Weight incorporation and loading efficiency of Gels 1, 2, and 3. (b) Percentage of the released model drug (fluorescein) at pH 3.0 and 7.4 after 24 h of incubation. (c) Released kinetics of Gel 2 at pH 3.0, pH 5.0, pH 7.4, and pH 7.4 with 0.1 M DTT. (d) Concentration-dependent viability of HeLa cells treated with different hydrogels over 24 h as determined by AlamarBlue assay. Error bars in (a-c), s.d. (n=3). Error bars in d, s.d. (n=5).

Table of Contents Entry

Hydrogels with dual responsiveness are prepared by EDC coupling of pH-responsive anionic pseudo-peptides as backbones and disulfide-containing L-cystine dimethyl ester as crosslinkers. These hydrogels show high loading efficiency, rapid but complete triggered-release and good biocompatibility, thus having potential applications for oral delivery.

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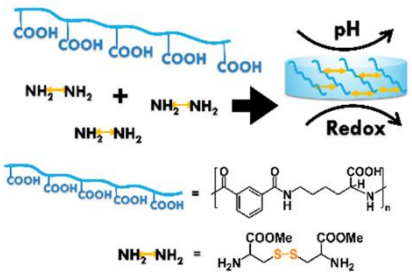

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