Customized Hydrogel for Sustained Release of Highly Water-Soluble Drugs

Xin Jin, Cheng-xiong Wei, Cheng-wei Wu, and Wei Zhang*

ABSTRACT: Highly water-soluble drugs, due to the rapid diffusion in water, are difficult to be released sustainably. To address the issue, a hydrogel with a core−shell structure is designed for the release of highly water-soluble drugs. The core is used to load the drug and the shell is devoted to isolating the drug from the release medium, which can decrease the drug concentration gradient and the driving force of drug release. The core−shell structure prolongs the drug release time by extending the drug release pathway. Moreover, the core−shell hydrogel possesses high swelling properties to reside in the stomach. The results demonstrate that the customized hydrogel can prolong the release of the highly water-soluble drug (metformin hydrochloride) for more than 50 h and alleviate the burst release of the drug.

INTRODUCTION

Highly water-soluble drugs are difficult to implement the long-term and sustained release due to the rapid diffusion in water. It will induce a serious physical burden and side effects for the human body. Generally, the modulation of the network of drug carriers or the enhancement of the interactions of the network with drugs can prolong the release time of drugs to some extent but usually less than 24 h. Simultaneously, the high concentration gradient of drugs between the drug carrier and the release medium is inevitable, which can cause a high driving force of drug release and induce the burst release of drugs. In response to this drawback, core−shell carriers are proposed as they enable the drug to be encapsulated in the core or evenly distributed between the core and shell, decreasing the driving force to prolong drug release time from the carrier. However, the retention time of the carrier in vivo is usually overlooked. The gastrointestinal transit time generally does not exceed 12 h, which means that the carrier may be expelled from the body without being released completely. Equally important, the retention time of the carrier in vivo should be prolonged to allow the drug to be released completely. Therefore, new strategies for the sustained release of highly water-soluble drugs are still desired.

Here, a customized hydrogel is proposed for controlled drug release and the prolongation of retention time in stomach. The core−shell structure of the hydrogel is used to extend the drug release pathway and reduce the concentration gradient of drugs. The core−shell hydrogel with high swelling properties has the potential to reside in the stomach. It is expected that the customized hydrogel can realize the sustained release of highly water-soluble drugs.

RESULTS AND DISCUSSION

For the sustained release of highly water-soluble drugs, a hydrogel with a core−shell structure is customized (Figure 1). The design of the core−shell structure is based on the prolongation of the retention time of the carrier and the release time of the drug. To prolong the retention time of the carrier, the core−shell hydrogel is designed as a swelling carrier to reside in the stomach. The sustained release of the drug is accomplished by the core−shell structure. The core is used to load drugs, and the shell can isolate the drugs from the release medium. This structure can effectively reduce the driving force of drug release by reducing the concentration gradient of drugs and prolong the release time by extending the drug release pathway.

The hydrogel consists of the core and the shell. The shell is a double network, the first network of polyacrylamide is formed by the polymerization of the acrylamide monomer. In Fourier transform infrared (FTIR) spectra (Figure 2a), the stretching vibration peak of acrylamide double bond (985.5 cm$^{-1}$) almost disappears after polymerization. The second network of polysaccharides is formed by ionic cross-linking of chitosan and sodium alginate. For the chitosan spectrum, the peaks at 1641 and 1592 cm$^{-1}$ represent the stretching vibration of amide I and the in-plane bending vibration of $\nu$NH$_2$, shifting to a high wavenumber by $\Delta/8$ cm$^{-1}$ and $\Delta/11$ cm$^{-1}$, respectively, in the shell, which indicates the possible ionic

Received: October 31, 2021
Accepted: January 27, 2022
Published: March 1, 2022
cross-linking of chitosan and sodium alginate. These results are supported by differential scanning calorimetry (DSC), as shown in Figure S1. For the sodium alginate spectrum, the peaks at 1593 and 1409 cm$^{-1}$ (Figure 2b) are due to asymmetric and symmetric stretching vibrations of $\text{COO}^-$, respectively. For the core, the peak at 1409 cm$^{-1}$ in sodium alginate shifts to 1417 cm$^{-1}$ after being immersed in the calcium chloride solution, indicating the substitution of sodium with calcium ions during the formation of the core. After being immersed in the simulated gastric fluid (SGF), the peak at 1593 cm$^{-1}$ in sodium alginate shifts to 1600 cm$^{-1}$. A plausible explanation is that protonated amino groups in chitosan are cross-linked with the carboxyl groups of sodium alginate to form new networks under the gastric acid.

The morphologies and the cross-section of the core–shell hydrogel are shown in Figure 2cd. The prepared core–shell hydrogel shrinks after dehydration and significantly swells after being immersed in SGF, which is conducive to the oral administration and subsequent gastric retention (Figure 2ef). The microscopic morphology of the core–shell hydrogel is observed using a scanning electron microscope (SEM). The shell network has a higher cross-linking degree and a thicker pore wall (Figure 2g). After being immersed in SGF, the pore size of the shell increases, and a new network forms with smaller pore size (Figure 2i). The core has a dense network without obvious pores (Figure 2h) but shows plenty of pores after being immersed in SGF (Figure 2j).

The cell biocompatibility of the core–shell hydrogel is characterized using a cell counting kit-8 (CCK-8). The result shows that the core–shell hydrogel has good biocompatibility to cells (HaCaT), and cell viabilities are greater than 95% (Figure 3a). The swelling behavior of the core–shell hydrogel in SGF is investigated. The result shows that the core–shell hydrogel can reside in the stomach because it swells to be larger than the diameter of the pylorus (12.8 ± 7 mm) within 60 min (Figure 3b). Subsequently, the core–shell hydrogel swells over time, and the volume variation and the swelling ratio can reach 6.5 (Figure 3c) and 730.1% (Figure 3d) at 72 h, respectively. High swelling behavior is in favor of the gastric retention of the hydrogel. The network of the polyacrylamide hydrogel (Figure 3e) exhibits the increasing pore size and

---

**Figure 1.** Schematic diagram of core–shell hydrogel design. AM, CS, and SA represent acrylamide, chitosan, and sodium alginate, respectively.

**Figure 2.** FTIR spectra of (a) shell and (b) core. Calcium alginate represents the reaction of sodium alginate in the core with calcium chloride. Photographs: (c) core–shell hydrogel; (d) cross-section of the core–shell hydrogel; (e) dehydrated core–shell hydrogel; and (f) core–shell hydrogel immersed in SGF for 72 h. Distance between adjacent scale marks: 1 mm. SEM images: (g) shell and (h) core and (i) shell and (j) core after being immersed in SGF for 72 h. Scale bar: 200 μm. The SEM image of the prepared core with high magnification is shown in Figure S2, Supporting Information.
loose structure after swelling (Figure 3f). The swelling behavior is largely ascribed to the hydrolysis and ionization of partial molecular chains of the polyacrylamide network in the shell.\textsuperscript{17,18}

However, polyacrylamide hydrogel with high swelling properties cannot resist gastric compression (Figure 4a). On this basis, the second network of polysaccharides forms in the shell, and the compressive stress of the shell at 60% strain is about 50 kPa (Figure 4b), indicating that the mechanical properties are improved by double networks. Furthermore, the mechanical stability of the hydrogel is an important factor in long-term gastric retention due to the presence of gastric contractions. The compressive stress of the core–shell hydrogel at 60% strain is about 55 kPa (Figure 4c). It
decreases to about 40 kPa after being immersed in SGF for 72 h (Figure 4d), which is still higher than the gastric pressure of humans (10–13 kPa). This result indicates that the mechanical strength of the core–shell hydrogel after swelling can resist gastric pressure and avoid being crushed.

Metformin hydrochloride has a short half-life, high water solubility, and usually requires frequent and high dosage administration. Therefore, the dosage of metformin hydrochloride has become the main cause of gastrointestinal intolerance. The smooth delivery of metformin hydrochloride will help avoid gastrointestinal intolerance. Moreover, according to the previous study, when chitosan is combined with metformin hydrochloride, chitosan can reduce the treatment dosage of metformin hydrochloride or act as a biological enhancer for metformin hydrochloride. This may be related to the inhibition of \( \alpha \)-amylase and \( \alpha \)-glucosidase by chitosan in type 2 diabetes patients. Here, the core–shell hydrogel containing chitosan is used for the sustained release of metformin hydrochloride. Compared with the single hydrogel core, metformin hydrochloride is sustainably released from the core–shell hydrogel (Figure 4e and f), and the release time can be prolonged to be more than 50 h without obvious burst release. The sustained release of metformin hydrochloride is mainly attributed to the core–shell structure of the hydrogel. The core–shell structure can reduce the drug concentration gradient and driving force of drug release to slow the release rate and alleviate the burst release of drugs. Another advantage of the core–shell structure is that it can prolong the drug release time by extending the drug release pathway. As such, metformin hydrochloride can be released sustainably from the core–shell hydrogel.

To investigate the release mechanism of metformin hydrochloride from the core–shell hydrogel, the Ritter-Peppas model, eq 1, is employed to fit the cumulative drug release curve. Initial 60% of the drug release is considered to be a valid kinetics model.

\[
\frac{M_t}{M_\infty} = k t^n
\]

where \( M_t \) and \( M_\infty \) are the quantity of metformin hydrochloride released at time \( t \) and total quantity of loaded metformin hydrochloride, respectively, \( t \) is the release time, \( k \) is a constant, \( n \) is the diffusion exponent characteristic of the release mechanism, and \( R^2 \) is the coefficient of determination. For the cylindrical hydrogel, when \( n = 0.45 \), it indicates the Fickian diffusion. When \( n = 0.89 \), it indicates the case II transport. When \( 0.45 < n < 0.89 \), metformin hydrochloride mainly releases through non-Fickian diffusion. The fitting results (Figure S4) of drug release are \( n = 0.458 \), \( k = 0.188 \), and \( R^2 = 0.972 \). The \( n \) value is very close to 0.45, indicating that Fickian diffusion takes the dominant role.

In summary, the customized hydrogel with a core–shell structure has a high swelling ratio, good cell biocompatibility, and stable mechanical properties. The volume variation and swelling ratio can reach 6.5 and 730.1% at 72 h, respectively. The compressive stress slightly decreases from 55 kPa to 40 kPa at 60% strain after being immersed in SGF for 72 h, which is higher than the gastric pressure of humans. The core–shell hydrogel possesses the capability of long-term gastric retention by swelling. More importantly, the core–shell structure reduces the release rate and prolongs the release time of drugs. The release time of metformin hydrochloride can be prolonged to be more than 50 h without obvious burst release. The core–shell hydrogel has the potentials to be used in the sustained release of highly water-soluble drugs.

### METHODS

**Preparation of the Core–Shell Hydrogel.** Preparation of the Shell. 3 g of acrylamide, 45 mg of \( N,N',N' \)-bis (acyrloyl) cystamine, 30 \( \mu \)L of \( N,N',N',N' \)-tetramethylethlenediamine, 0.9 g of chitosan, 0.9 g of sodium alginate, and 60 mg of ammonium persulfate were mixed in 30 mL of aqueous solution containing 30% (v/v) ethanol. The mixed solution was heated at 60 °C for 60 min to form the gel. Then, the gel was immersed in a 0.5 mol L\(^{-1} \) hydrochloric acid aqueous solution for 24 h to form the shell.

**Preparation of the Core.** 1 g of chitosan and 1 g of sodium alginate were dispersed into 10 mL of deionized water. The mixture was immersed in a 5% (w/v) calcium chloride solution for 5 min to form the core.

**Assembly of the Hydrogel.** The customized core was sealed into the customized hollow shell, and the edge was bonded with biological adhesive (3 M Vetbond, USA).

**Characterization of the Core–Shell Hydrogel.** The morphology of the core–shell hydrogel was observed on a SEM (FEI Quanta 200, USA). The formation of the core–shell hydrogel was characterized by FTIR (Thermo Nicolet iN10, USA) and DSC (TA Instruments Q2000, USA). The swelling properties were characterized by a swelling ratio and volume variation \( V_t/V_0 \). The compression properties were measured on the pressure sensor loaded with a 500 N load cell (C43, MTS, China). The cell biocompatibility of the core–shell hydrogel was evaluated using CCK-8. The drug release was measured on the UV–vis spectrophotometer (UV 1800, Shimadzu, Japan). The detailed experiments are presented in the Supporting Information.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c06106.

Additional DSC of the formation of the shell, SEM image of the prepared core, stepwise release of metformin hydrochloride from the core–shell hydrogel, fitting curve of drug release from the core–shell hydrogel, and experimental details and materials (PDF)

### AUTHOR INFORMATION

**Corresponding Author**

Wei Zhang – State Key Laboratory of Structure Analysis for Industrial Equipment, Department of Engineering Mechanics, Dalian University of Technology, Dalian 116024, China; Email: weizhang@dlut.edu.cn

**Authors**

Xin Jin – State Key Laboratory of Structure Analysis for Industrial Equipment, Department of Engineering Mechanics, Dalian University of Technology, Dalian 116024, China; orcid.org/0000-0002-3672-6853

Cheng-xiong Wei – State Key Laboratory of Structure Analysis for Industrial Equipment, Department of Engineering Mechanics, Dalian University of Technology, Dalian 116024, China
Cheng-wei Wu — State Key Laboratory of Structure Analysis for Industrial Equipment, Department of Engineering Mechanics, Dalian University of Technology, Dalian 116024, China

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c06106

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Key R&D Project of China (2018YFA0704103 and 2018YFA0704104), NSFC of Liaoning Province (2019-KF-02-01), and Fundamental Research Funds for the Central Universities (DUT20YG129 and DUT21TD105).

■ REFERENCES

(1) Bonnet, F.; Scheen, A. Understanding and overcoming metformin gastrointestinal intolerance. Diabetes, Obes. Metab. 2017, 19, 473–481.
(2) Bailey, C. J. Metformin: historical overview. Diabetologia 2017, 60, 1566–1576.
(3) Kikuchi, S.; Takayama, K. Multivariate statistical approach to optimizing sustained-release tablet formulations containing diltiazem hydrochloride as a model highly water-soluble drug. Int. J. Pharm. 2010, 386, 149–155.
(4) Xuan, B.; Wong, S. N.; Zhang, Y.; Weng, J.; Tong, H. H. Y.; Wang, C.; Sun, C. C.; Chow, S. F. Extended release of highly water soluble isoniazid attained through cocryostabilization with curcumin. Crys. Growth Des. 2020, 20, 1951–1960.
(5) Razavi, M.; Karimian, H.; Yeong, C. H.; Fadaeinassab, M.; Khang, S. L.; Chung, L. Y. D.; Haron, D. E. B. M.; Noordin, M. I. Gastroretentive behavior of orally administered radiolabeled tamarind seed formulations in rabbits validated by gamma scintigraphy. Drug Des. Dev. Ther. 2017, 11, 1–15.
(6) Bera, H.; Kumar, S.; Maiti, S. Facile synthesis and characterization of tailor-made pectin-gellan gum-bionanofiller composites as intragastric drug delivery shuttles. Int. J. Biol. Macromol. 2018, 118, 149–159.
(7) Mullarney, M. P.; Seery, T. A. P.; Weiss, R. A. Drug diffusion in hydrophobically modified N, N-dimethylacrylamide hydrogels. Polymer 2006, 47, 3845–3855.
(8) Huang, X.; Brazel, C. S. Analysis of burst release of proxphylline from poly (vinyl alcohol) hydrogels. Chem. Eng. Commun. 2003, 190, 519–532.
(9) Zhang, W.; Jin, X.; Li, H.; Wei, C.-x.; Wu, C.-w. Onion-structure bionic hydrogel capsules based on chitosan for regulating doxorubicin release. Carbohydr. Polym. 2019, 209, 152–160.
(10) Guo, T.; Zhang, N.; Huang, J.; Pei, Y.; Wang, F.; Tang, K. A facile fabrication of core-shell sodium alginate/gelatin beads for drug delivery systems. Polym. Bull. 2019, 76, 87–102.
(11) Wooster, T. J.; Acquistapace, S.; Mettraux, C.; Donato, L.; Dekkers, B. L. Hierarchically structured phase separated biopolymer hydrogels create tailorable delayed burst release during gastrointestinal digestion. J. Colloid Interface Sci. 2019, 553, 308–319.
(12) Khan, F.; Bera, D.; Palchaudhuri, S.; Bera, R.; Mukhopadhyay, M.; Dey, A.; Goswami, S.; Das, S. Dual release kinetics in a single dosage from core-shell hydrogel scaffolds. RSC Adv. 2018, 8, 32695–32706.
(13) Yan, F.; Zheng, C.; Zhai, X.; Zhao, D. Preparation and characterization of polyacrylamide in cationic microemulsion. J. Appl. Polym. Sci. 1998, 67, 747–754.
(14) Wang, H.; Gong, X.; Miao, Y.; Guo, X.; Liu, C.; Fan, Y.-Y.; Zhang, J.; Niu, B.; Li, W. Preparation and characterization of multilayer films composed of chitosan, sodium alginate and carboxymethyl chitosan-ZnO nanoparticles. Food Chem. 2019, 283, 397–403.
(15) Najafi-Soulari, S.; Shekarchizadeh, H.; Kavir, M. Encapsulation optimization of lemon balm antioxidants in calcium alginate hydrogels. J. Biomater. Sci., Polym. Ed. 2016, 27, 1631–1644.
(16) Kopplin, G.; Lervik, A.; Draget, K. I.; Achmann, F. L. Alginate gels crosslinked with chitosan oligomers—a systematic investigation into alginate block structure and chitosan oligomer interaction. RSC Adv. 2021, 11, 13780–13798.
(17) Zhou, Y.; Jin, L. Hydrolysis-induced large swelling of polyacrylamide hydrogels. Soft Matter 2020, 16, 5740–5749.
(18) Xu, S.; Wang, Y.; Hu, J.; Liu, Z. Atomic understanding of the swelling and phase transition of polyacrylamide hydrogel. Int. J. Appl. Mech. 2016, 08, 1640002.
(19) Houghton, L. A.; Read, N. W.; Heddle, R.; Maddern, G. J.; Dowton, J.; Touli, J.; Dent, J. Motor activity of the gastric antrum, pylorus, and duodenum under fasted conditions and after a liquid meal. Gastroenterology 1988, 94, 1276–1284.
(20) Davidson, J.; Howlett, H. New prolonged-release metformin improves gastrointestinal tolerability. Br. J. Diabetes Vasc. Dis. 2004, 4, 273–277.
(21) Arun, G.; Rajaram, R.; Kaleshkumar, K.; Gayathri, N.; Sivasudha, T.; Kandasamy, S. Synergistic effect of novel chitosan combined metformin drug on streptozotocin-induced diabetes mellitus rat. Int. J. Biol. Macromol. 2020, 153, 1335–1349.
(22) Brazel, C. S.; Peppas, N. A. Modeling of drug release from swellable polymers. Eur. J. Pharm. Biopharm. 2000, 49, 47–58.
(23) Inal, M.; Işıkalan, N.; Yüjiçoğlu, M. Preparation and characterization of pH-sensitive alginate-g-poly (N-vinyl-2-pyrrolidone)/gelatin blend beads. J. Ind. Eng. Chem. 2017, 52, 128–137.
(24) Costa, P.; Sousa Lobo, J. M. Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci. 2001, 13, 123–133.