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Resistant starch as a carrier for oral colon-targeting drug matrix system

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Abstract In this study, a novel tablet of protein drug matrix for colon targeting was developed using resistant starch as a carrier prepared by pre-gelatinization and cross-linking of starch. The effects of pre-gelatinization and cross-linking on the swelling and enzymatic degradation of maize starch as well as the release rate of drug from the matrix tablets were examined. Cross-linked pre-gelatinized maize starches were prepared by double modification of pre-gelatinization and cross-linked with $POCl_3$, and bovine serum albumin was used as a model drug. For in vitro drug release assays, the resistant starch matrix tablets were incubated in simulated gastric fluid, simulated intestinal fluid and simulated colonic fluid, respectively. The content of resistant starch and swelling property of maize starch were increased by pre-gelatinization and cross-linking, which retarded its enzymatic degradation. Drug release studies have shown that the matrix tablets of cross-linked pre-gelatinized maize starch could delivery the drug to the colon. These results indicate that the resistant starch carrier prepared by pre-gelatinization and cross-linking can be used for a potential drug delivery carrier for colon-targeting drug matrix delivery system.

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Introduction

There has recently been increasing interest in targeting peptide and protein drugs to the colon because of the relatively low activity of proteolytic enzymes in the colon. Based on these finding, many oral colon-targeting drug delivery systems have been examined for the specific delivery of these drugs to the colon [1–2]. Therefore, it is necessary and urgent to develop novel carriers in the field of pharmacy [3–6].

Starches can be easily modified and are highly stable, safe, nontoxic, good film forming and in addition biodegradable, which suggests their use in targeted drug delivery systems. Problem encountered with the use of starches is their easy digestibility by the enzyme and acid in the upper digestive tracts. An ideal approach is to modify the structure of starch to improve starch resistance to digestion and make starch escaping enzymatic digestion and acidolysis in upper digestive tracts but being degraded by microorganism in colon. These modified starches are called Enzyme-Resistant starches [7]. It was reported previously from our laboratory that resistant starch is a potential carrier for oral colon-targeting drug delivery [8]. Oral colon-targeting drug delivery systems for bovine serum albumin (BSA) were developed using resistant starch as coating films. This study has been intending to develop novel protein drug matrix tablets used for colon targeting, in particularly the effect of resistant starch prepared by pre-gelatinization and cross-linking on swelling and enzymatic degradation of

maize starch, and to evaluate the drug release rate from the resistant starch matrix.

Materials and methods

Materials

Maize starch was obtained from Staple Starch Co. (Guangzhou, China). Bovine serum albumin (BSA) with a Mw of 67,000 was obtained from Boao biotechnology Co. (Shanghai, China). Resistant Starch-based carriers were prepared by starch double modification of pre-gelatinization and cross-linked with $POCl_3$ in our lab [9].

Methods

Characterization of cross-linked pre-gelatinized starch

The sample was pretreated with pronase and then the resistant starch (RS) content was determined according to the Method 991.43 total dietary fiber of the Association of Official Analytical Chemists [10]. The cross-linking degree was expressed as mole of substituent phosphorus content per mole of anhydroglucose unit. The substituent phosphorus content was evaluated by the method of Smith and Caruso [11]. To investigate the swelling property of different cross-linked pre-gelatinized starches in the simulated gastrointestinal tract, swelling ratio was determined as Moussa method [12]. In the method, the samples were incubated at 37 °C for 2 h in simulated gastric fluid (SGF) and 6 h in simulated intestinal fluid (SIF). The swelling ratio was calculated by W_S/W_D. where W_S and W_D are the weights of the swollen and dry cross-linked pre-gelatinized starch after treatment, respectively. The crystal morphology of cross-linked pre-gelatinized starch was identified by an X-ray diffractometer (D-max IIIA, Rigaku, Japan).

In vitro drug release studies

Dry-coated matrix tablets consisted of a core and cross-linked pre-gelatinized starch shell. The core weighed 80 mg and consisted of 50% of BSA and 50% of cross-linked pre-gelatinized starch. The BSA and cross-linked pre-gelatinized starch were mixed manually in a mortar and were compressed at 1500 kg/cm^2 at room temperature. Once the core was compressed and then dry-coated with the shell that weighed 120 mg, and consisted either of 100% cross-linked pre-gelatinized starches with different DC. All tablets prepared were 5 mm in diameter. The drug release from compressed cross-linked pre-gelatinized starch matrix tablets was carried out using a drug dissolution rate test apparatus 2(100 rpm, 37 °C) according to the USP23. Freshly prepared SGF [13] was used as the dissolution medium for the first 2 h and then replaced with freshly prepared SIF [12] for the 6 h. Afterward, the dissolution medium was replaced with simulated colonic fluid (SCF) (pH 7.0 PBS) for an additional 28 h. At the end of the each time period, two aliquots (1 mL each) were taken, suitably diluted. The supernatant was filtered through a bacteria-proof filter and the filtrate was analysed for BSA amount using Bradford method [14].

Results and discussion

RS analysis and cross-linked pre-gelatinized starch swelling

Table 1 showed the RS content of pre-gelatinized starch and the cross-linked pre-gelatinized starches with different degree of cross-linking (DC) by the TDF method. The enzymatic degradation was considerably retarded through increasing the degree of cross-linking of pre-gelatinized starch. The RS content of the modified maize starch was increased as the degree of cross-linking increased. The results showed that the resistant starch content of cross-linked pre-gelatinized starch could reach above 90% when the degree of cross-linking (DC) was 0.030.

The swelling ratios of the cross-linked pre-gelatinized starch particles after incubations in SGF and SIF were higher than those of the corresponding pre-gelatinized starch (see Fig. 1). The maximum swelling power in the case of low DC (DC < 0.0057) could increase 100% compared with pre-gelatinized starch. In the higher DC the swelling power decreased as the DC increased. The non-monotonic variation of the swelling ratio with DC is a particular characteristic of the cross-linked pre-gelatinized starch matrix that differs from those of other classical polymeric matrices for which increasing DC lead to lower swelling ratio. This behavior of cross-linked pre-gelatinized starch was ascribed to the particular structure where, in the case of low DC, phosphodiester group is hydrophilic so starch granules become more easily to bind with water and easily to swollen and in the case of high DC, covalent

Table 1 The relationship between degree of cross-linking and RS content

Sample	Degree of cross-linking	RS content (%)
1#	0.00	0.68 ± 0.1
2#	0.0032	1.77 ± 0.5
3#	0.0057	3.59 ± 1.0
4#	0.024	34.4 ± 1.2
5#	0.030	94.6 ± 1.5
6#	0.099	99.2 ± 1.4

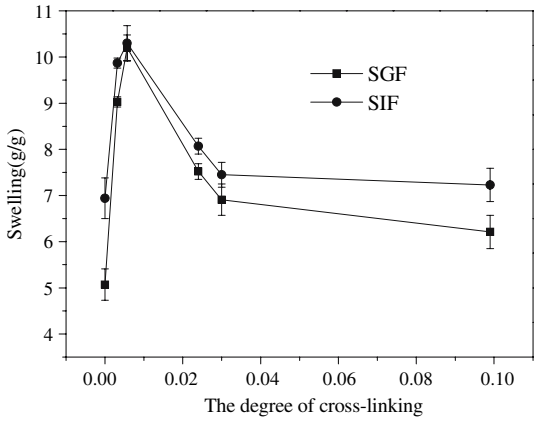

Fig. 1 Swelling ratios of cross-linked pre-gelatinized starches in SGF and SIF

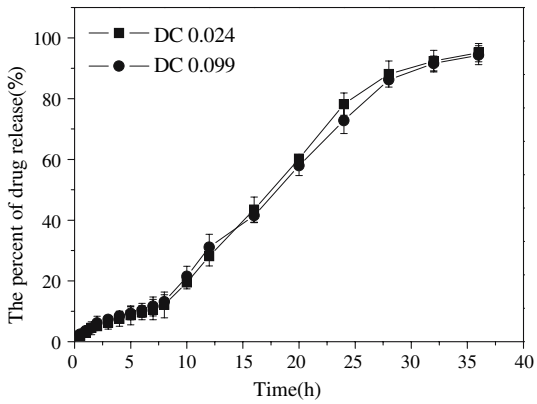

Fig. 3 BSA release (%) from cross-linked pre-gelatinized starch matrix tablets with different DC in SGF for the first 2 h and then in SIF for 6 h and then in SCF for the additional 28 h

linkages of cross linking, interchain hydrogen bonds, and water-promoted hydrogen associations stabilize the network, thus controlling the access of water into the matrix. All the matrix tablets from compressed cross-linked pre-gelatinized starch didn't disintegrate in 24 h.

Microstructure and crystal morphology of cross-linked pre-gelatinized starch

The X-ray diffraction spectra of cross-linked pre-gelatinized starches powder showed differences with varying DC (see Figs. 2). Maize starch shows typical crystal morphology of A-type double-helix structure [15]. For the cross-linked pre-gelatinized starch polymers, with increasing DC the intensity of peaks at 2θ = 15°, 17°, 18° and 23° diminished, whereas the peak at 2θ = 19.0°–19.7° became more important as the starch digestion resistance increased. This peak is characteristic of V-type single-helix structure [16]. So the crystal morphology of cross-linked pre-gelatinized starch became V-type polymorph and the molecular structure changed from double-helix structure to single-helix structure compared with the maize starch as the starch digestion resistance increased.

The colon-targeting of cross-linked pre-gelatinized starch and BSA release

To study the colon-targeting of cross-linked pre-gelatinized maize starch matrix systems, a core consisting mainly of the model drug was compressed and then the core is dry-coated with cross-linked pre-gelatinized maize starch polymer. The outer cross-linked pre-gelatinized maize starch shell is a gel-forming matrix layer, and the core is the drug reservoir containing BSA. The release of BSA

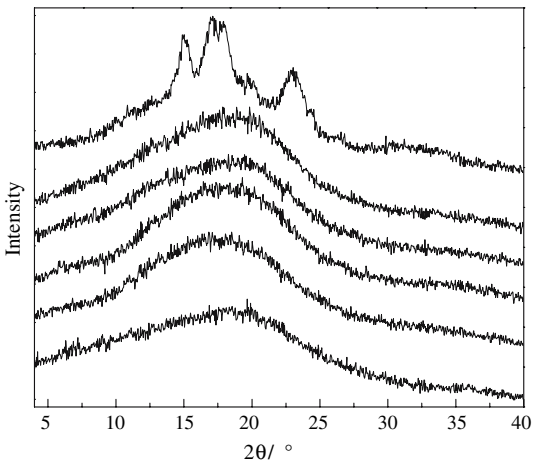

Fig. 2 The XRD patterns of cross-linked pre-gelatinized starches with different DC (from top to bottom: maize starch, pre-gelatinized starch, DC 0.0032, DC 0.0057, DC 0.024, DC 0.099)

Table 2 Regression equation of BSA release from the cross-linked pre-gelatinized starch matrix tablets with different DC

The matrix tablets with different DC	Regression equation	Correlation coefficient (R^2)
0.024	$Q = 0.0467t^{0.862}$	0.975
0.099	$Q = 0.0759t^{0.853}$	0.993

Table 3 Regression equation of drug release kinetics of BSA at different media of cross-linked pre-gelatinized starch -based matrix tablets with DC 0.024

Media	Regression equation	Correlation coefficient (R^2)
SGF	$Q = 0.9403t^{0.333}$	0.987
SIF	$Q = 0.5242t^{0.481}$	0.992
SGF	$Q = 0.0696t^{0.897}$	0.991

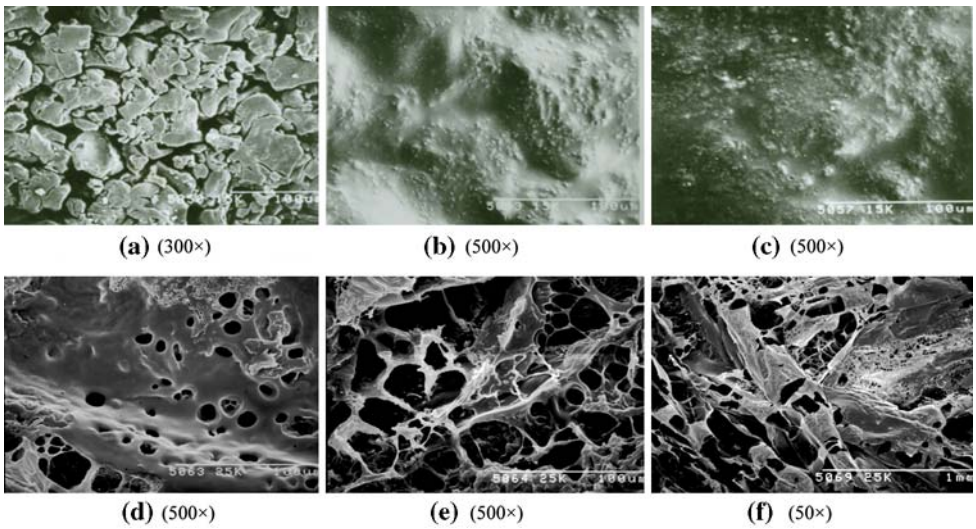

Fig. 4 The surface of starch-based BSA matrix tablet after drug releasing for (**a**) 0 min, (**b**) 2 min, (**c**) 2 h, (**d**) 8 h, (**e**) 12 h and (**f**) 24 h. The DC of the cross-linked pre-gelatinized starch used in the matrix tablet is 0.024

occurs by its dissolution at the shell-core interface and its diffusion through the polymeric gelled membrane. The BSA release properties of the matrix tablets from cross-linked pre-gelatinized maize starch showed that this matrix tablet drug delivery system had a good ability of drug colon-targeting release. It is seen from Fig. 3 that about 10% of BSA was released from the tablet after 8 hr of incubation. This indicated that BSA matrix tablets compressed by cross-linked pre-gelatinized maize starch could successfully pass through the upper gastrointestinal tract. Over a period of 36 hr the release was above 90% (see Fig. 3). There is no appreciable difference of release kinetics for the two different cross-linking degrees. The reason may be the swelling ratio of the two cross-linked pre-gelatinized maize starches has no significant difference in the SGF and SIF (Fig. 1).

In order to describe the drug release from the tablets of cross-linked pre-gelatinized maize starch matrix, the Ritger-Peppas equation (Eq. 1) was adapted to the observed data.

$$Q = Kt^n (1)$$

Where Q is the amount of drug released at time t, k is a constant incorporating structural and geometric characteristic of the device, and n is the release exponent, indicative of the mechanism of drug release. For the tablets when the exponent $n < 0.45$, the drug release is controlled by the diffusion and when $n > 0.89$ the drug release is controlled by the matrix erosion. Values of n between 0.45 and 0.89 can be regarded as an indicator for the superposition of both phenomena.

From the Correlation coefficient showed in the Table 2, the kinetic model for drug release was in agreement with Ritger-Peppas equation. The release exponents from the matrix tablets with two DC are between 0.45 and 0.89 indicating the drug released in total 36 h was controlled by the superposition of the diffusion and erosion. In order to investigate the different release mechanism at the different location of the simulated gastrointestinal tract, the regression equations of drug release kinetics of BSA in SGF, SIF and SCF were also obtained by Eq.(1) respectively. From the release exponent in the Table 3, it concluded that the BSA release was controlled by diffusion in SGF and by the superposition of the diffusion and erosion in SIF, while chiefly by erosion in SCF. From the Fig. 4 it also can be seen the same conclusion.

Conclusion

The tablets from cross-linked pre-gelatinized maize starch matrix have a good ability of colon-targeting release. The BSA release was controlled by the superposition of the diffusion and erosion. In SGF the drug release is mainly controlled by diffusion and by the superposition of the diffusion and erosion in SIF, while chiefly by erosion in SCF. In conclusion, resistant starch-based carrier materials for oral colon-targeting drug delivery system can be produced by double starch modification of pre-gelatinization and cross-linking. The cross-linked pre-gelatinized maize starch oral colon-targeting matrix tablet has a potential as a new oral dosage form for targeting peptide and protein drugs.

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