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Evaluation of amorphous debranched starch as extended-release matrices in tablets

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ABSTRACT

This study aims to investigate the physicochemical and extended-release properties of amorphous debranched starch (ADBS) that is a linear short chain amylose derived from pullulanase enzymatic modification. The results show the completely amorphous ADBS was soluble in cold water, which developed into a disordered gel network at 25 °C. ADBS based tablets were able to extend drug release in different media. Drug release, which was accelerated by decreased pH and pancreatin, was barely affected by ionic strength. The kinetics of the drug release process that was dominated by Fickian diffusion was best fitted and interpreted by the Higuchi equation. The results indicate ADBS is an ideal hydrophilic excipient which extends the in vitro release of water-soluble drugs for 24 h.

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1. Introduction

Starch and its derivatives have been widely used as natural and safe tablet excipients in pharmaceutical formulations for more than forty years. Native starch (NS) consists of two α-D-glucose polymers, i.e. linear amylose (20–30%) and branched amylopectin (70–80%) (Al-Karawi & Al-Daraji, 2010; Pohja, Suihko, Vidgren, Paronen, & Ketolainen, 2004). In general, NS is utilized as filler, binder, as well as disintegrant in the solid dosage form. However, it cannot be used as the excipient in extended-release tablet due to its low compactibility and elastic compression behavior. Additionally, NS is prone to being eroded by pancreatin in the gastrointestinal tract, leading to the failure of extended drug release (Prado, Matulewicz, Bonelli, & Cukierman, 2009).

The deficiency of NS can be remedied by being modified (Lemieux, Gosselin, & Mateescu, 2009). Considerable starch derivatives have been introduced into drug delivery systems to effectively extend release with the development of starch modification technology and pharmaceutical industry. For example, physically modified starches (e.g. high pressure autoclave, osmotic pressure treatment, extrusion, planetary mill, roll drying or spray drying), chemically modified starches (e.g. oxidation, esterification, etherification, hydroxypropylation, reductive amination, succinylation, etc.), as well as enzymatically hydrolyzed starches (e.g. dextrin or debranching starch) have been used as the excipients for extended-release tablets (Andersson, Rydberg, Larsson, Andersson, & Aman, 2002; Chou, Wu, Nurtama, & Lin, 2010; Fornal et al., 2012; Kapusniak, Jochym, Bajer, & Bajer, 2011; Limberger, da Silva, Emanuelli, Comarela, & Patias, 2008; Song, Min, Hwang, & Lee, 2008; Waliszewski, Aparicio, Bello, & Monroy, 2003).

So far as we know, only the extended-release characteristics of chemically modified starches have been thoroughly accessed compared with which the more secure enzymatically hydrolyzed starches have seldom been studied. NS is a semi-crystalline polymer with the crystallinity of approximately 45% (Cai, Shi, Rong, & Hsiao, 2010). The crystal structure of NS can be substantially melted by gelatinization before enzymatic hydrolysis. The branching points in both amylose and amylopectin can be highly cleaved by pullulanase (Manners, 1989), after which NS is altered into a mixture of long and short linear chains which is genuinely pure low-molecular-weight amylose.

Low-molecular-weight amylose is partially soluble in aqueous medium. Thus, the solubility of enzymatically modified starch debranched by pullulanase is remarkably elevated. Both the solubility and the amorphous structure of enzymatically modified starch determine the formation of gel network. The associated amorphous and non-ordered starch chains develop into a non-ordered gel network which is resistant to the erosion of gastrointestinal enzyme that thus favors extended drug release.

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The digestibility of pullulanase debranched starch has also been investigated. The contents of slowly digestible starch (SDS) and resistant starch (RS) reached to 60–80% (Cai & Shi, 2010; Cai et al., 2010; Miao, Jiang, & Zhang, 2009). Accordingly, we conclude that amorphous debranched starch (ADBS) modified by pullulanase is a suitable extended release candidate and a feasible excipient for direct compression matrix tablets. Thereby motivated, the present work targets to determine the physicochemical properties of ADBS and the impacts on their extended-release characteristics, as well as to clarify the mechanism of drug release from enzymatically modified starch based matrix tablets.

2. Materials and methods

2.1. Materials

Corn starch was provided by Zhucheng Xingmao Corn Development Co., Ltd. (batch No. 79696, Shandong, P.R. China). Promozyme D2 (EC 3.2.1.41) was obtained from Novozymes (batch No. ATS20036, Tianjin, P.R. China). Erioglaucine disodium salt (batch No. MKBH5342V, soluble in water at 18.7 g/100 ml at 21 °C, MW 792.85, $c = 10^{-3}$–1.0 mg/ml, a blue and clear solution) and pancreatin (batch No. SLBC2100V) were purchased from Sigma–Aldrich Chemical Co. (St. Louis, MO, USA). All the other chemicals used in this study were of analytical grade.

2.2. Methods

2.2.1. Preparation of ADBS

ADBS was prepared by the modified method of Cai et al. (Cai, Bai, & Shi, 2012). 10% (w/v) maize starch slurry (0.01 M, pH 5.5, acetic acid buffer) in a pressure tube (ACE Glass, Vineland, NJ, USA) was cooked in a boiling water bath with stirring for about 15 min. Then the pressure tube was transferred to a hot air oven (DHG-9055A, Yiheng Scientific Instrument Co., Ltd., Shanghai, P.R. China) and thoroughly gelatinized at 130 °C for 1 h. Promozyme D2 (1% based on the dry weight of starch) was added after the starch paste was cooled to 55 °C. The mixture was debranched at 55 °C with stirring for 24 h. Thereafter the enzymolysis liquid was freeze-dried (Labconco Co., Kansas, MO, USA), yielding debranched starch (DBS). Then DBS (5 g, dry basis) was dissolved in an alkaline solution (50 ml, 1 M NaOH solution) and neutralized by 1 M HCl. The dissolved starch was precipitated by being slowly added into 1500 ml of anhydrous ethanol with continuous stirring. After the mixture was stored at room temperature overnight, the precipitate was collected and vacuum dried (DZG-6050, Senxin Experimental Instrument Co., Ltd., Shanghai, P.R. China) at 40 °C by decanting the supernatant. Finally, the product was acquired and stored.

2.2.2. Light microscopy

The morphological structure of the starch samples was analyzed using an Olympus BX41TF light microscope (Olympus Co., Tokyo, Japan). NS and ADBS were dispersed in distilled water and anhydrous ethanol respectively. A drop of starch dispersion was added in the middle of the microscope slide with a coverglass thereon. The samples were observed with normal light and polarized light, and the images were recorded at 400× magnification.

2.2.3. X-ray diffraction analysis

X-ray diffraction analysis was examined using an X-ray powder diffractometer (ARX-400, Bruker AXS Co., Germany). The starch powders were scanned at the rate of 1°/min from 5° to 40° (2θ) at 35 kV and 20 mA with Cu-Kα radiation ($\lambda = 1.5406$ Å) at room temperature.

2.2.4. Solubility test

The solubility of the starch samples was measured as follows. A precisely weighted starch sample (0.1 g, dry basis) was mixed with 9.9 ml of deionized water, which was shaken for 30 min in a water bath shaker at 30 °C, 50 °C, 70 °C, 90 °C and 100 °C, respectively. The mixture was centrifuged at 5000 rpm for 15 min (RJ-LD-IIB, Ruijiang Instruments Co., Ltd., Jiangsu, P.R. China), and the supernatant was dried in a hot-air oven at 105 °C until a constant weight. The solubility of the starch samples was calculated according to Eq. (1).

$$\text{solubility}(\%) = \frac{W_1}{W_0} \times 100\% \quad (1)$$

where W_1 is the dry residue weight of the supernatant liquid, and W_0 is the dry basic content of the starch samples.

2.2.5. Rheological properties

The rheological properties of the starch samples were analyzed on a TA AR1000 rotational rheometer (TA instruments, New Castle, DE, USA) with a 40-mm flat-plate system. The flat gap was 1 mm.

Starch dispersion (10%, w/w) was gelatinized in a boiling water bath for strain sweep and frequency sweep. The starch paste was transferred to the flat-plate system before it was cooled, and the edge of the sample was covered with a thin layer of low-weight silicon oil to prevent moisture loss. Strain sweep was measured at the constant frequency of 1 rad/s over the strain range of 0.1%–100% at 30 °C to determine the linear viscoelastic region of the samples. Frequency sweep was made at an appropriate strain within the linear viscoelastic region at 30 °C over the frequency range of 0.1–100 rad/s.

The formation and stability of gel network were determined by time sweep and temperature sweep. Starch slurry (30%, w/w) was tested on the flat-plate system, and the sample at the edge of the flat-plate was covered by silicon oil. Time sweep was measured at 25 °C and the frequency of 1 rad/s for 2 h. Subsequently, temperature sweep was measured at the frequency of 1 rad/s and at a strain within the linear viscoelastic region. The temperature was raised from 25 °C to 90 °C at the rate of 1 °C/min.

The rheological properties of the starch samples were expressed as storage modulus (G') and loss modulus (G'').

2.2.6. Tablets preparation

Drug (Erioglaucine disodium salt, 2%, w/w) and ADBS powders (98%, w/w) were thoroughly mixed in a sealed plastic box. Tablets (250 mg) were prepared by being dry-blended and directly compressed at 15 kN using a 10-mm flat faced tooling on hydraulic press (769YP-15A, Tianjin Keqi High & New Technology Co., Tianjin, P.R. China).

2.2.7. In vitro release studies

The in vitro controlled-release properties of the ADBS based tablets were assessed by a simulated USP XXIII dissolution apparatus No. 2. The dissolution tests were performed in 900 ml of dissolution medium with the paddle rotation speed of 50 rpm at 37 °C. Dissolution samples (2 ml) were measured using a UV–visible spectrophotometer (Alpha-1860A, Puyuan Instruments Co., Ltd., Shanghai, P.R. China) at 625 nm at appropriate time intervals. Linearity between 0 and 25 μg/ml: $r^2 = 0.9988$; precision RSD (%) values: around 5%.

Exploring the kinetics and mechanism of drug release is able to correlate the in vitro and in vivo performances. The drug release data were fitted to zero-order (Eq. (2)), first-order (Eq. (3)), Higuchi (Higuchi, 2006) (Eq. (4)), Peppas (Peppas, 1985) (Eq. (5)) and Peppas and Sahlin equations (Peppas & Sahlin, 1989) (Eq. (6)), yielding the

optimal mathematical model. Different equations were used to fit the release data ranging from 5% to 60%.

$$\frac{M_t}{M_\infty} = kt \tag{2}$$

$$\frac{M_t}{M_\infty} = 1 - e^{kt} \tag{3}$$

$$\frac{M_t}{M_\infty} = kt^{1/2} \tag{4}$$

$$\frac{M_t}{M_\infty} = kt^n \tag{5}$$

$$\frac{M_t}{M_\infty} = k_d t^m + k_r t^{2m} \tag{6}$$

where M_t/M_∞ is the fractional drug released at time t, k is the kinetic constant, and n is the diffusional exponent describing the kinetics of drug release. The values of $n < 0.45$, $0.45 < n < 0.89$, $n = 0.89$ and $n > 0.89$ indicate Fickian diffusion, anomalous (non-Fickian) transport, case-II transport and Super Case II transport (Ritger & Peppas, 1987), respectively. Besides, k_d and k_r are the diffusion and relaxation rate constants respectively, and m is the purely Fickian diffusion exponent for any geometrically shaped device capable of controlled release. For Eq. (6), the value of m is 0.445 ($2a/l = 3.815$, where $2a$ is the diameter and l is the thickness of the tablets). The first term in the right-hand side of Eq. (6) is the Fickian contribution, and the second term is the Case-II relaxational contribution. The percentage of drug release originating from the Fickian mechanism (F) was used to evaluate the importance of the two mechanisms in the overall release behavior (Peppas & Sahlin, 1989). F can be readily calculated as:

$$F = \frac{1}{1 + k_r/k_d t^m} \tag{7}$$

Moreover, different release profiles were compared using the similarity factor f_2 calculated by Eq. (8):

$$f_2 = 50 \cdot \log \{[1 + (\frac{1}{n})\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \cdot 100\} \tag{8}$$

where R_t and T_t are the percentages released at each time point. An f_2 value between 50 and 100 implies the similarity between two release profiles (FDA, 1997).

2.2.8. Statistical analysis

All the experiments were carried out in duplicate or triplicate. The average and standard deviation of the experimental data were used to denote the results and significant variability in quantitative analysis respectively. MS Office Excel 2003 (Microsoft Co., Redmond, WA, USA), IBM SPSS® Amos™ 19 (SPSS Inc., Chicago, IL, USA) and OriginPro 8.0 (OriginLab Co., Northampton, MA, USA) were employed for statistical analysis and illustration drawing.

3. Results and discussion

3.1. Crystal structure and morphology characterization

The micromorphology and crystal structure of NS and ADBS were observed by a light microscope with normal light and polarized light (Fig. 1). Most native maize starch granules are spherical and polygonal (Fig. 1A). A characteristic birefringence pattern with a Maltese cross can be discerned under the polarized light (Fig. 1a), which can be attributed to the differed density and refractive index of ordered crystal structure and disordered amorphous one inside the starch granules because NS is a semicrystalline polymer. The shape and structure of the NS starch granules were distorted after modification (Fig. 1B). Besides, the disappearance of the Maltese cross indicates the ordered crystal structure was transformed into disordered amorphous one (image not shown).

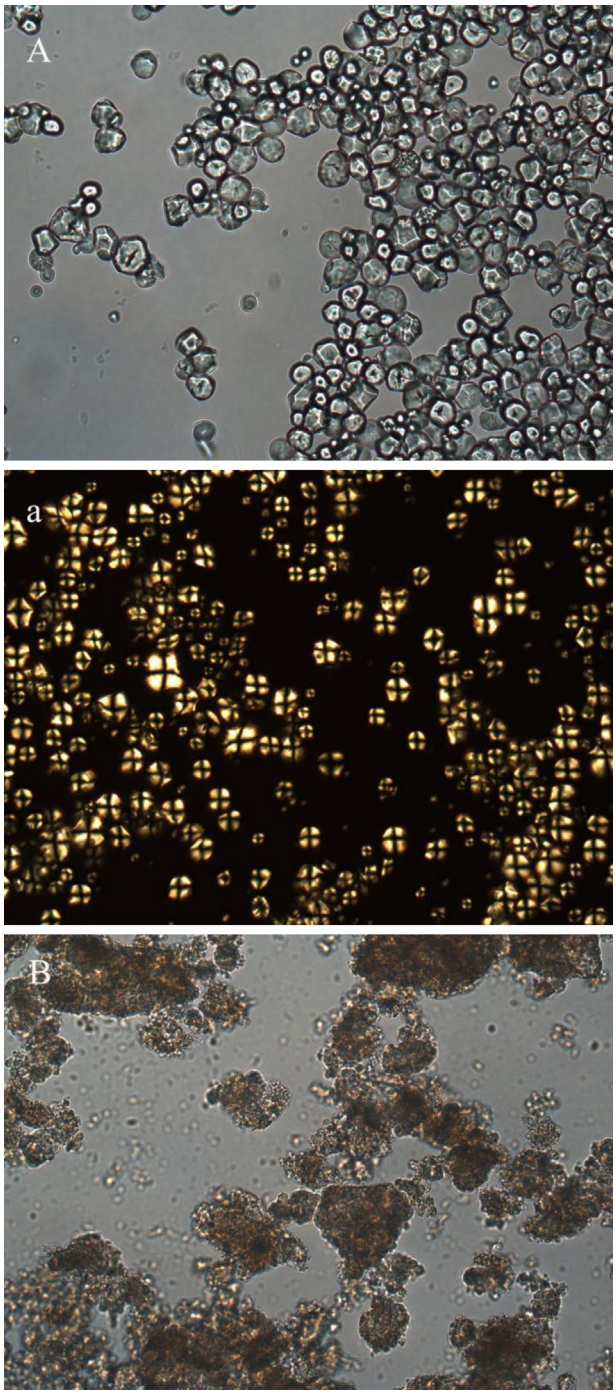

Fig. 1. Light microscopy micrograph of the native starch (NS) (A, a) and amorphous debranched starch (ADBS) (B) with normal light (A, B) and polarized light (a).

The crystal structures of NS and ADBS were further explored by X-ray diffraction (Fig. 2). The NS powders exhibit four intense peaks at around 15.3°, 17.1°, 18.2° and 23.5°, which is an evident A-type diffraction pattern. The crystalline structure of starch granule was entirely disrupted by being enzymatically modified and dissolved in the alkaline solution, leading to an amorphous X-ray diffraction pattern instead. The results of both light microscopy micrograph and X-ray diffraction suggest the enzymatically debranched starch was a completely amorphous derivative.

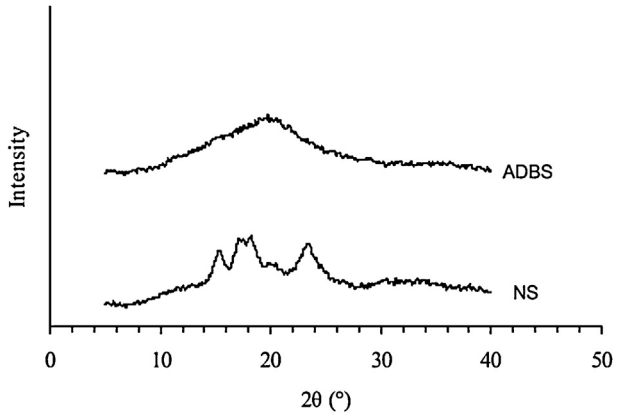

Fig. 2. X-ray diffraction patterns of NS and ADBS.

3.2. Solubility of starch powders

Fig. 3 presents the solubility of ADBS and NS powders at different temperatures. Pullulanase enzymatic modification apparently increased the solubility of NS powders in distilled water at each temperature. The NS powder, which was insoluble in cold water, began to dissolve 70 °C. However, the solubility of ADBS powder exceeded 60% readily in cold water. The significant difference results from the altered crystalline structure and chain length distribution of starch molecules. ADBS is a completely amorphous polymer, the crystalline structure of which was thoroughly disrupted by being dissolved in sodium hydroxide solution. Simultaneously, pullulanase enzymatically hydrolyzed the α-1, 6 glycosidic bonds of amylopectin selectively, which thus produced linear short chain amylose. The amorphous structure and the linear short chain amylose synergetically elevated the solubility of ADBS obviously. As an extended-release tablet excipient, the solubility in cold water determines both the formation of gel network and the sustained release properties of tablets.

3.3. Rheological properties

3.3.1. Strength of gel network

Dynamic rheometer has been applied to study the viscoelastic or rheological properties of the starch samples during gelatinization and the aging of starch gels (Hsu, Lu, & Huang, 2000; Lii, Tsai, & Tseng, 1996; Tsai, Li, & Lii, 1997). The strength of the gel network when the starch paste was cooled down was investigated (Fig. 4A–D). Storage modulus (G') represents the energy stored in the material and the recovered one per cycle, and loss modulus

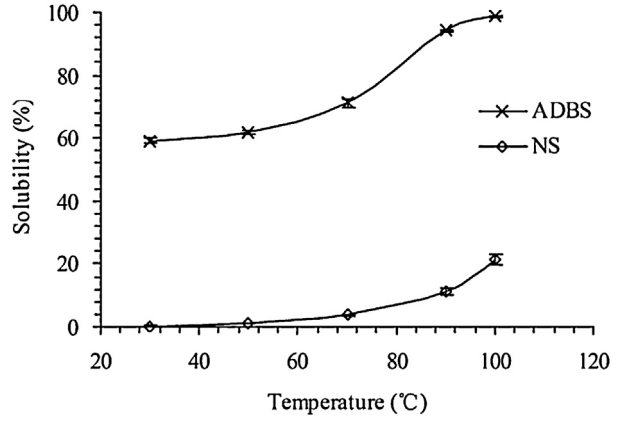

Fig. 3. Solubility (%) of NS and ADBS at different temperatures.

Table 1
Similarity factors (f_2) of drug release from ADBS based tablets in different media.

Medium factor	Comparison	f_2	Result
pH	pH 1.2–pH 5.4	56.16	Similar
	pH 1.2–pH 6.8	54.28	Similar
	pH 1.2–pH 7.4	53.03	Similar
	pH 5.4–pH 6.8	88.34	Similar
	pH 5.4–pH 7.4	81.87	Similar
	pH 6.8–pH 7.4	87.33	Similar
Ionic strength	0.1 M–0.2 M	82.38	Similar
	0.1 M–0.3 M	83.44	Similar
	0.2 M–0.3 M	94.92	Similar
Pancreatin	Without pancreatin	48.53	Dissimilar

(G'') represents the energy dissipated or lost per cycle of sinusoidal deformation (Ferry, 1980; Singh, Singh, Kaur, Singh Sodhi, & Singh Gill, 2003).

The linear viscoelastic region of the starch paste was identified during strain sweep test (Fig. 4A and B). Suitable strain values of both NS and ADBS were selected within the linear ranges. The NS and ADBS pastes were subjected to frequency sweep test at the strains of 0.1 and 0.005, respectively.

The two pastes also behaved significantly differently during the frequency sweep test (Fig. 4C and D). The ADBS paste was of higher G', G'' and tan δ values than the NS paste. The results indicate that the ADBS paste composed a stronger and more viscous gel network than the NS paste did. The moduluses (G', G'') of these two samples increased slightly with increasing frequency.

The gelatinization and aging of starch paste are controlled by chain length, molecular weight as well as the ratios of amylose to amylopectin and crystalline to amorphous (Tester, 1997), which were altered tremendously after the enzymatic modification by pullulanase. The branched starch macromolecules were decomposed into linear short chain amylose confronting the α-1, 6 glycosidic bonds being enzymatically hydrolyzed. The starches comprising more amylose were of higher G' and G'' values (Kaur, Singh, & Sodhi, 2002). The ADBS paste was more subject to being transformed into gel network due to the reinforced association between starch chains.

3.3.2. Formation ability and stability of gel network

The aqueous suspension of NS granules could not be evolved into a disordered gel network during the time sweep test at 25 °C. The order-disorder transitions during the time and temperature sweeping tests of the ADBS suspension (w/w, 30%) were investigated (Fig. 4E and F).

A stable gel network formed after 45 min of time sweep (Fig. 4E). The G' and G'' values decreased with increasing temperature, suggesting that the gel network was undermined. Fig. 4F shows that the ADBS sample underwent gel–sol transition at 50 °C. Linear short chain amylose plays an essential role in the construction of gel network. Unlike multibranched amylopectin, ADBS can be partially dissolved in cold water. The linear short amylose chains remain mobile, which benefits the reassociation between starch chains. The formation of gel network in cold water intrinsically favors the extended-release property of ADBS based tablets.

3.4. Release studies

3.4.1. Effect of pH

The processes of drug release from ADBS based tablets at pH 1.2, 5.4, 6.8 and 7.4 were investigated. Different release profiles were compared using similarity factor (f_2), and the results are shown in Table 1. Fig. 5A infers that the pH of dissolution medium merely impacts drug release slightly, which was accelerated with

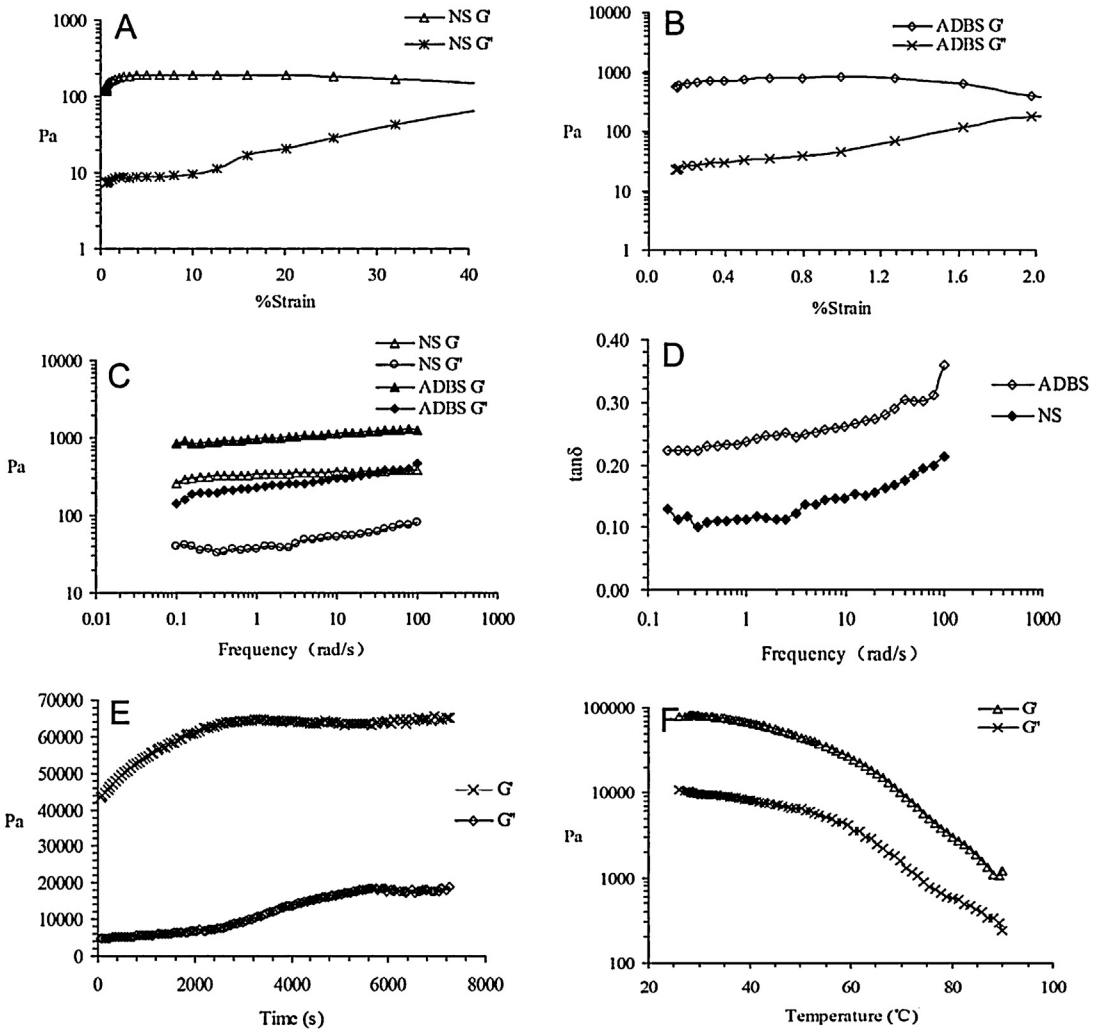

Fig. 4. Rheological properties of ADBS and NS: (A) strain sweep curve of NS; (B) strain sweep curve of ADBS; (C) G' and G'' values of NS and ADBS during the frequency sweep; (D) loss factor (tan δ) of NS and ADBS during the frequency sweep; (E) G' and G'' values during time sweep of ADBS suspension; (F) temperature sweep of the ADBS based gel network.

decreasing pH. The f_2 values ranging between 53.03 and 88.34 indicate the drug release profiles were similar in the media at different pH. Relatively speaking, drug release was accelerated in simulated gastric fluid (SGF, pH1.2) compared to those at pH 5.4, 6.8 and 7.4 (f_2 = 53.03–56.16 respect to 81.87–88.34). The phenomenon may be attributed to the degradation of starch molecules in the acidic medium. It has been confirmed that starch molecules can be dissolved in alkaline medium, while starch macromolecules are degraded into micromolecules in acidic medium. Although the degradation was aggravated in SGF, the ADBS based tablets could still extend the release of drugs.

3.4.2. Effect of ionic strength

The effect of ionic strength was studied (Fig. 5B) in the phosphate buffer (SIF, pH 6.8) into which were added appropriate amounts of sodium chloride. The drug release from ADBS based tablets remained intact at the ionic strength ranging from 0.1 to 0.3 mol/L. Besides, the results also reveal that drug release was shielded from the influences of osmotic pressure and diets (f_2 = 82.38–94.92).

3.4.3. Effect of pancreatin

The effect of pancreatin on the in vitro drug release of ADBS based tablets in simulated intestinal fluid (SIF, pH6.8) was investigated (Fig. 5C). An f_2 value of 48.53 suggests that the release profiles with or without pancreatin were dissimilar. Adding pancreatin into SIF remarkably accelerated the release, which can be ascribed to the enzymatic hydrolysis of pancreatic α-amylose to ADBS. Moreover, the modified starch was hydrolyzed into other polysaccharides, oligosaccharides and monosaccharides. Fortunately, the drug release from ADBS based tablets was effectively protected from enzymatic erosion. The ADBS based tablets could still control the drug release continuously over 8 h in the SIF with pancreatin, suggesting that they were able to endure the erosion of gastrointestinal enzymes.

3.5. Drug release mechanism and kinetics study

To understand the drug release mechanism and kinetics from HPMC- and ADBS-based tablets, the drug release data ($5\% \leq M_t/M_\infty \leq 60\%$) were fitted to zero-order, first-order, Higuchi, Peppas, and Peppas and Sahlin equations, respectively. The different kinetic constants are listed in Table 2. Hydroxypropylmethyl cellulose (HPMC) has been demonstrated as a hydrophilic excipient similar to ADBS (Michailova, Titeva, Kotsilkova, Krusteva, & Minkov, 2001; Peerapattana, Phuvarit, Srijesdaruk, Preechagoon, & Tattawasart, 2010). The release profiles of HPMC- and ADBS-based tablets were compared using the similarity factor (f_2). An f_2 value of 59.52 indicates the drug release profile of ADBS based tablets

Table 2
Mathematical modeling and drug release kinetics of ADBS and HPMC based tablets.

Tablets	Zero-order	First-order	Higuchi	Peppas		Peppas and Sahlin		
	Fit factors	Fit factors	Fit factors	n	Fit factors	k_d	k_r	Fit factors
ADBS	$r^2 = 0.9868$ $r^2_{adj} = 0.9850$ $F = 526.37$	$r^2 = 0.9953$ $r^2_{adj} = 0.9946$ $F = 1481.14$	$r^2 = 0.9956$ $r^2_{adj} = 0.9950$ $F = 1589.42$	0.4345	$r^2 = 0.9922$ $r^2_{adj} = 0.9911$ $F = 893.32$	0.0237	0.0001	$r^2 = 0.9991$ $r^2_{adj} = 0.9989$ $F = 4160.00$
HPMC	$r^2 = 0.9812$ $r^2_{adj} = 0.9786$ $F = 366.01$	$r^2 = 0.9952$ $r^2_{adj} = 0.9945$ $F = 1452.90$	$r^2 = 0.9962$ $r^2_{adj} = 0.9957$ $F = 1863.61$	0.6031	$r^2 = 0.9934$ $r^2_{adj} = 0.9925$ $F = 1054.78$	0.0154	0.0007	$r^2 = 0.9993$ $r^2_{adj} = 0.9992$ $F = 5334.26$

resembled that of HPMC based ones. A gel layer is developed on the surface of HPMC based tablets in the case of being exposed into an aqueous medium. The gelatinous surface barrier critically controls drug release and withstands the erosion of gastrointestinal enzymes. In addition, HPMC based tablets were used for comparison because HPMC is an ideal hydrogel matrix. The determination coefficients (r^2), the adjusted coefficient of determination (r^2_{adj}) and the F-ratio (F) of the above mathematical models are shown in Table 2.

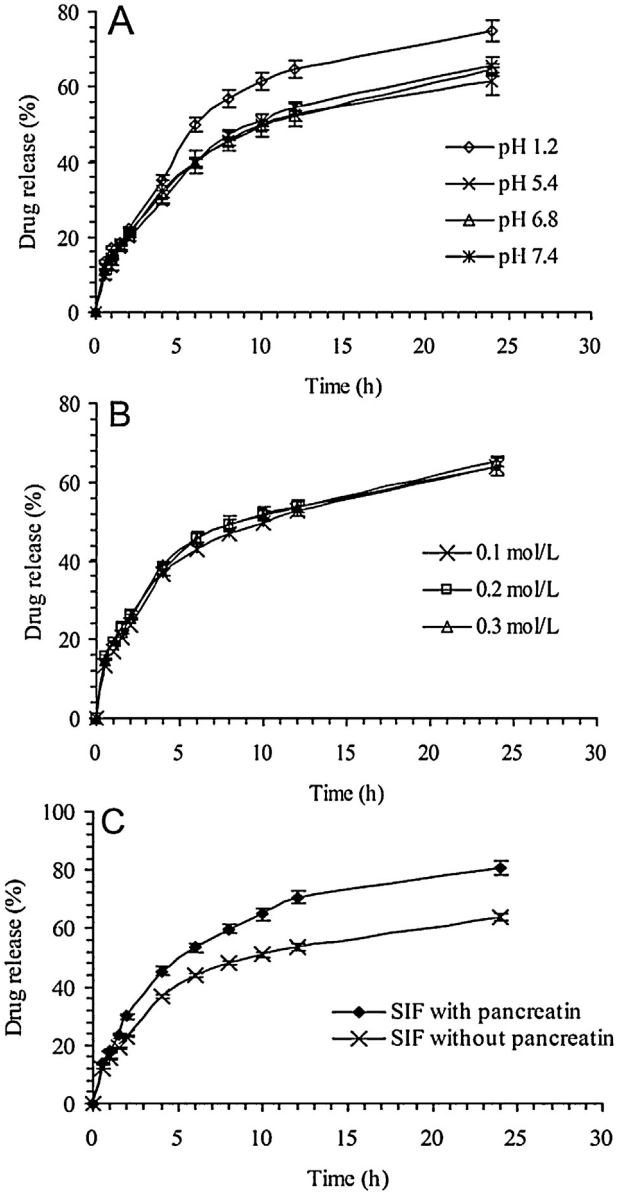

Fig. 5. Influence of the release medium on drug release process from ADBS based tablets: (A) pH; (B) ionic strength; (C) pancreatin.

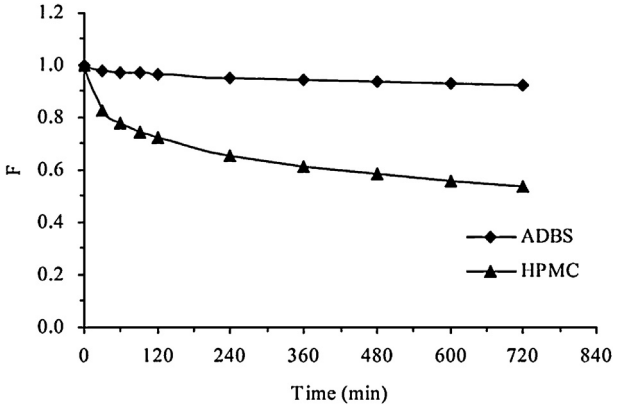

Fig. 6. Fickian release fraction (F) of ADBS and HPMC based tablets.

The in vitro drug releases of both ADBS and HPMC based tablets were best fitted and explained by Higuchi equation with the r^2_{adj} values of 0.9950 and 0.9957 respectively. Peppas as well as Peppas and Sahlin equations were used to speculate the mechanism of drug release. The n values of ADBS and HPMC based tablets were 0.4345 and 0.6031 respectively. Therefore, ADBS and HPMC based tablets were transported following the Fickian diffusion and anomalous (non-Fickian) release respectively. The percentage of drug release stemming from the Fickian mechanism (F) was used to evaluate the importance of Fickian release in the overall drug release behavior (Fig. 6). The results reveal drugs were released from HPMC based tablets via the cooperation between diffusion and erosion ($F > 0.464$). The in vitro drug release of ADBS based tablets was more prone to being controlled by diffusion than that of the HPMC based ones was. The Fickian release predominated in the overall release behavior of ADBS based tablets ($F > 0.903$).

4. Conclusions

In this study, the physicochemical and extended-release features of ADBS were investigated. We found that the enzymatically debranched starch was a completely amorphous starch derivative. A gel layer was developed on the surface of the tablet derived from ADBS which was a hydrophilic matrix once being exposed into the aqueous medium. Different factors of the dissolution medium, such as pH and pancreatin, prominently influenced the extended drug release. However, the release rate was rarely affected by ionic strength. We confirm that the drug release from ADBS tablets was a diffusion-controlled release (Fickian diffusion) on the basis of elaborately studied mechanism and kinetics. The drug release data were optimally fitted to the Higuchi equation. The results herein suggest the pullulanase modified starch is a feasible hydrophilic and hydrogel-forming matrix candidate in extended-release tablets. Further studies on the in vivo extended-release properties of ADBS

based tablets in experimental rabbits as well as the in vitro–in vivo correlation (IVIVC) analysis are still ongoing.

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