AAPS PharmSciTech (2020) 21: 55
DOI: 10.1208/s12249-019-1549-y

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Research Article

Effect of Sodium Alginate Type on Drug Release from Chitosan-Sodium Alginate–Based *In Situ* Film-Forming Tablets

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Received 8 June 2019; accepted 23 September 2019; published online 6 January 2020

Abstract. Natural polymers are promising as the carrier of matrix-based sustained release tablets but limited by their diversity in source and structure properties. Our previous studies found that chitosan (CS)- and alginate (SA)-based tablets can form self-assembled polyelectrolyte complex (PEC) film on the surface, which controlled drug release with a novel mechanism. To elucidate whether PEC-based sustained drug delivery system could weaken the influence of single-matrix material diversity on drug release behavior, taking theophylline as a drug model, the effect of SA structure properties, including viscosity, G/M ratio, SA salt type, and degree of esterification on drug release profiles, swelling, and erosion of CS-SA composite system was investigated. The results showed that the viscosity, G content, salt type, and esterification degree of SA had a remarkable influence on drug release when SA alone was used as a matrix, but little effect of these parameters on drug release was observed in CS-SA combination system. SA of low viscosity is superior in controlling drug release from CS-SA combination system. Potassium, magnesium salt of SA, and esterified SA can help form PEC of higher thickness with different swelling and erosion extent. In conclusion, this study demonstrated that drug release diversity due to SA structure difference can be well eradicated by using CS-SA combination system, which is a promising strategy to manufacture natural polymer-based products with constant quality.

KEY WORDS: chitosan; alginate; diversity; polyelectrolyte complex (PEC); sustained release.

INTRODUCTION

Oral-sustained release preparations have long been popular in the pharmaceutical field because of their advantages of reducing dosing frequency, prolonging drug absorption time, improving patient compliance, and ensuring the safety of medication and so on. And matrix-based sustained-release tablets are widely used in manufacturing, mainly due to its simple preparation process, low requirements on equipment, low production cost, and easy industrialization (1). Natural polymers, including chitosan and alginate, are promising as the carrier of matrix-based sustained release tablets with low cost and good safety profile. However, due to their diversity in source and different structure properties, their reproducibility in controlling drug release behavior might be affected when used alone, influencing their broad application in large-scale manufacturing despite their numerous advantages. Solving this problem may not only lead to remarkable decrease in manufacture cost but also more high-quality products in the market.

According to previous studies, the cationic polymers and anionic polymers have developed a new mechanism for controlling drug release behavior because they can self-assembly on the tablets' surface to form polyelectrolyte complex (PEC) films (2–4). The system can regulate drug release behavior via reducing the tablets' erosion and swelling, with sustained drug release behavior more stable than using single polymers. The most widely used cationic polymer is chitosan. It is derived from chitin deacetylation with good biocompatibility, non-toxicity, and biodegradability (5–7). Since its pKa is about 6.5, it is protonated in acidic conditions to produce positively charged NH^{3+} and easy to form PEC with anionic polymers (8,9). Alginate (SA), an anionic polymer, is formed by linking α-L-guluronic (G) and β-D-mannuronic acid (M) through 1,4-glycosidic bonds (10). It may have a different structure due to a wide variety of brown algae sources and different extraction methods (6,11,12). G and M are distributed in the molecular chain of SA with an irregularly arranged order (10). The pKa of SA is between 3.4 and 4.4. Therefore, it is insoluble in acid and forms a insoluble framework structure (12), which can extend drug release in the stomach. It is negatively charged in the intestine and can form PEC with CS there.

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CS-SA-based matrix tablets have been proved to form PEC under the conditions of simulated gastrointestinal fluid, which can achieve nearly zero-order sustained release of theophylline for 12 h (2). Influence of drug properties on CS-SA sustained released behavior has been explored (3). However, the previous study mainly focused on the fundamental mechanism of CS-SA-sustained released system and expand their application for different drugs, where SA with specific properties were used. It is unclear whether structure diversity of SA can influence the properties of PEC member thus affect sustained-release ability from the CS-SA complex system. Therefore, in this study, 10 types of SA were selected to elucidate the effect of SA structure characteristics on release behavior of theophylline from the CS-SA system and understand drug release mechanism by investigating their swelling and erosion properties. Taking theophylline (TH) as a drug model, the effect of SA structure properties, including viscosity, G/M ratio, SA salt type, and degree of esterification on drug release profiles, swelling, and erosion in CS-SA matrix tablets were investigated. Thereafter, the applicability of the CS-SA combination system to sustain the release of drugs with different properties was evaluated.

MATERIALS AND METHODS

Materials

Theophylline (TH), venlafaxine hydrochloride (VH), and metformin hydrochloride (MH) were obtained from Tianjin Zhongan Pharmaceutical Co., Ltd (China), Guilin Huaxin Pharmaceutical Co., Ltd (Guangxi, China), and Zhuhai Yuancheng Pharmaceutical Chemical Co., Ltd (Guangdong, China), respectively. Chitosan with molecule weight of 400 kDa and deacetylation degree of 86.5% was supplied by Jinan Haidebei Marine Bioengineering Co., Ltd (China). Alginate and microcrystalline cellulose of type Avicel PH-101 were donated by FMC Biopolymer (Philadelphia, USA). Magnesium stearate was sourced from Anhui Shanhe Pharmaceutical Excipients Co., Ltd. (China). All other reagents were of analytical grade.

Preparation of Matrix Tablets

The prescription consisted of the model drug, polymer (CS, SA), filler (microcrystalline cellulose), and lubricant (magnesium stearate). The matrix tablets were prepared using direct powder compression method in this experiment. Briefly, the drug and all other excipients were firstly passed through an 80-mesh sieve. Then, based on the composition of the prescription, the drug was uniformly mixed with all the other excipients except for lubricant in a mortar, thereafter 0.3% magnesium stearate was added and blended for 1–2 min. Finally, the tablets were directly prepared using a type DP30A single-punch tableting machine (Beijing Gylongli Science & Technology Co., Ltd (China)) with flat-faced punch of 10-mm diameter. All tablets' hardness was adjusted to 40–80 N. Unless specially indicated, to maintain the surface area and volume unchanged, the final tablet mass was kept at 310 mg, and the total amount of polymer in the fixed prescription was 150 mg, the mass ratio of CS: SA was maintained at 1:1, with 150 mg model drug, 10 mg MCC, and 0.9 mg magnesium stearate in each tablet. To study the effect of drug properties on the release behavior of the CS-SA system, the total amount of polymer was 225 mg and the model drug in each tablet was 75 mg.

Erosion and Swelling Studies

During the dissolution process, the weight of tablets might change due to the penetration of medium and the dissolution of matrix. Thus, for the CS-SA combination system, swelling and erosion behaviors were calculated by the weighing method. Specific test methods were as follows: The tablet was weighed and placed in a dissolution tester from Shanghai Huanghai Instruments (ZRD6-B, China) using basket method (Chinese Pharmacopoeia of 2015) at 37.0 ± 0.5°C rotating at 100 rpm. In the first 2 h, 500 mL of pH 1.2 HCl solution (SGF, 0.1 N) was selected as the release medium, thereafter 500 mL of pH 6.8 phosphate buffer (SIF, 0.05 N) was used as the release medium, and the experiment was continued for 22 h. The tablets were taken out of the vessels at 1, 2, 4, 6, 8, 10, 12, and 24 h, respectively. Weighed the tablets immediately after surface moisture of the tablets was removed, and then the swollen tablets were dried at 60°C for 48 h until the weight did not change and the dried tablets were taken out for weighing. This experiment used a vernier caliper to roughly measure the film thickness of the CS-SA combination system after 24 h.

The erosion and the remaining ratios were calculated by Eq. (1) and Eq. (2), and the swelling ratio was calculated by Eq. (3) (13,14):

$$\mathrm{ER}(\%) = \frac{W_0 - W_r}{W_0} \times 100 \tag{1}$$

$$\mathrm{RM}(\%) = 100 - \mathrm{ER} \tag{2}$$

$$\mathrm{SR}(\%) = \frac{W_t - W_r}{W_r} \times 100 \tag{3}$$

In the above formula, *ER* is the ratio of dissolution, *RM* is the proportion of tablet residue, *SR* is the proportion of swelling (water absorption), W_0 is the initial dry tablets mass, W_r is the weight of remaining dry tablet after swelling at time t, and W_t is the weight of the swollen matrix tablet at time t. All test samples were calculated in triplicate.

In Vitro Release Studies

According to *in vitro* release method described in the Chinese Pharmacopoeia 2015, the *in vitro* release of tablets was carried out using basket method, with the drug dissolution apparatus from Shanghai Huanghai Instruments (ZRD6-B, China). If not specified, the release medium was 500 mL of SGF (0.1 N) at 0–2 h, then 500 mL of SIF (0.05 mol/L) was used as the release medium, and the study was continued for

22 h at 37.0 ± 0.5°C, with rotation speed at 100 rpm to simulate the transition of tablets through the gastrointestinal tract (15). Sample 10-mL medium at 1, 2, 3, 4, 6, 8, 10, 12, and 24 h immediately replenishes the corresponding fresh medium of equal volume. Filtered the samples with a 0.8-μm Millipore membrane and UV-visible spectrophotometer was used to analyze TH/VH/MH content in both media at wavelength 276/272/233 nm (Shanghai UNIC Instrument Corporation (UV-2000, China)), respectively. Since the absorbance of MH in SGF was relatively low, the samples were analyzed at 233 nm after dilution with SIF (3).

Difference between release curves was analyzed by similarity factor method (f_2), and the formula is in Eq. (4):

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (4)$$

In the above formula, R_t and T_t are the cumulative release rate of the reference and the test preparation at time t respectively, n is the number of sampling points. The release behaviors were significantly different if $f_2 < 50$ (16). However, when using this formula, it should be noted that there should be no more than one sampling point where the cumulative release (%) of the tested or the reference preparation is more than 85%.

In addition, drug release rate in SGF and SIF were calculated separately. $k_{1.2}$ was obtained by calculating the slope of dissolution curve in 0-2 h, and the slope of 2-24 h was defined as $k_{6.8.}$ All the test samples were calculated in triplicate and standard deviations were calculated.

Mathematical Fitting of the Release Profiles

Analysis of Drug Release Kinetics

For the prepared matrix tablets, drug release kinetics was usually fitted by the first-order release model (Eq. (5)) and Higuchi model (Eq. (6)) (17):

$$\frac{M_t}{M_\infty} = 1 - e^{-k_1 t} \quad (5)$$

$$\frac{M_t}{M_\infty} = k_2 t^{1/2} \quad (6)$$

In the equation, M_t and M_∞ are the cumulative release rate at time t and after infinite time respectively, k_1 and k_2 are the release constants.

Analysis of Drug Release Mechanism

For polymer matrix tablets, the release mechanism could be described by the Ritger-Peppas equation (Eq. (7)) (18).

$$\frac{M_t}{M_\infty} = kt^n \quad (7)$$

In the formula, k is a constant, relating to structure and geometry of the preparations, t is the drug release time, n is the release (diffusion) index describing the drug release mechanism. For cylindrical preparations, $n < 0.45$ indicates that it is Fickian diffusion, $0.45 < n < 0.89$ means that the dissolution and diffusion mechanisms are jointly controlled (non-Fickian diffusion mechanism), $n > 0.89$ means matrix erosion, that is, case II transport. It should be noted that this equation can only be used when the data of M_t/M_∞infinity is less than 0.6.

RESULTS AND DISCUSSION

When CS-SA combination system was used as a sustained-release carrier, the structural properties of SA might affect the thickness, mechanical strength, and compactness of the PEC film formed on the surface of tablets, which in turn change the controlled-release ability (19). Properties of different types of SA used in this study are shown in Table I.

Influence of SA Viscosity

The viscosity of polymer is closely related to its gel strength. Alginate of different viscosity can be easily obtained by oxidative degradation (20). By keeping the G content the same, influence of SA viscosity on TH release behavior was investigated. As shown in Fig. 1a, when SA alone was used as the matrix material, its viscosity influenced drug release behavior significantly. SA of low viscosity can only sustain the release of TH for 4 h, while SA of the highest viscosity prolonged TH release for up to 8 h, but SA of medium viscosity sustained drug release for approximately 6 h. It was noted that when SA alone was used as the matrix material, some cracks were observed on the surface of tablets in SGF, which might be one of the main reasons for the fast drug release.

SA in combination with CS led to remarkable improvement in drug release behavior. See in Fig.1b, despite of the type of SA used, the release amount in the first 4 h had no significant difference ($f_2 > 50$). And after 4 h, an interesting phenomenon was observed. The formulation containing the lowest viscosity of SA showed the lowest drug release while the prescription containing the highest viscosity of SA presented the fastest drug release rate, with the SA medium viscosity samples in between. Since SA and CS based *in situ* PEC film cannot be formed completely before 4 h (3), therefore it is reasonable that the release behavior was comparable at this time period. After 4 h, the properties of PEC film formed by CS-SA may have important effect on controlling drug release rate. It seems that PEC film formed by low-viscosity SA was more compact compared with that of high viscosity ones, probably the long chains of high-viscosity SA prevent its electrostatic interaction with CS due to steric effect, leading to leaky film formation. Therefore, in CS-SA combination system, SA of low viscosity is beneficial in controlling drug release.

For CS-SA combination system, to further elucidate how the SA viscosity affected the mechanism of drug release, its swelling and erosion were investigated. As shown in Fig. 1c, the swelling rate was faster at 0–4 h, and slowed

Table I. Properties of different types of SA

Types	Viscosity	G content	State	Degree of esterification
Viscosity				
Manucol LD	4–12 mPa*s in 1% solution	37–40%	Sodium salt	Non
Protanal CR8133	15–45 mPa*s in 1% solution	37–40%	Sodium salt	Non
Protanal LF120M	70–150 mPa*s in 1% solution	35–45%	Sodium salt	Non
Protanal LF200M	200–400 mPa*s in 1% solution	35–45%	Sodium salt	Non
Protanal CR8223	300–450 mPa*s in 1% solution	37–40%	Sodium salt	Non
G/M ratio				
Protanal LFR 5/60	3.5–7 mPa*s in 1% solution	65–75%	Sodium salt	Non
Manucol LD	4–12 mPa*s in 1% solution	37–40%	Sodium salt	Non
Salt type				
Protanal LF200M	200–400 mPa*s in 1% solution	35–45%	Sodium salt	Non
KF200FTS	200–400 mPa*s in1% solution	60–70%	Potassium salt	Non
Protanal LFMg 5/60	150–250 mPa*s in 1% solution	65–75%	Magnesium salt	Non
Protanal PH1033	500–1000 mPa*s in 0.5% solution	37–40%	Sodium and calcium salt	Non
Degree of esterification				
Kelcoloid K3B426	50–100 mPa*s in 1% solution	37–40%	Sodium salt	50–60%
Protanal CR8133	15–45 mPa*s in 1% solution	37–40%	Sodium salt	Non

down at 4–12 h due to formation of PEC film and kept almost constant thereafter, and the swelling ratio increased in SA viscosity–dependent manner. As for the erosion behavior of tablets (Fig. 1d), after 4 h, the erosion rate of low-viscosity SA containing system was faster than of the high-viscosity SA containing system, with 10% difference in remaining ratio. Meanwhile, to probe the potential influence of PEC film on tablet surface on drug release, thickness of the film was measured, it was 1.52 ± 0.05 mm, 1.51 ± 0.03 mm, 1.45 ± 0.06 mm, 1.57 ± 0.09 mm, and 1.57 ± 0.07 mm for CS-SA (CR8133), CS-SA (LF120M), CS-SA (LF200M), CS-SA (CR8233), and CS-SA (LD), respectively. The comparable film thickness indicated it is not the main reason for different drug release behavior. This study indicated that the faster drug release from high-viscosity SA containing system might contribute to its high swelling ratio, making the drug substance more permeable compared to less swelled system.

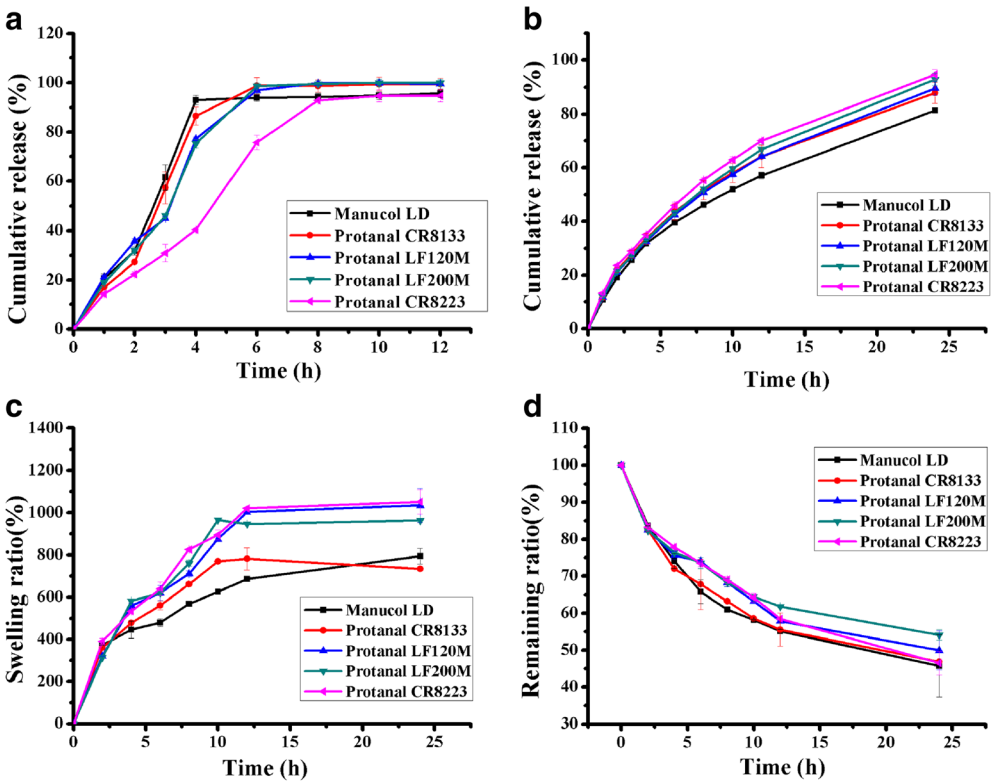

Fig. 1. Influence of SA viscosity on TH release from tablets based on **a** SA and **b** CS-SA, and **c** swelling and **d** erosion behavior of CS-SA (1:1) tablets in SGF followed by SIF

Influence of the SA G/M Ratio

Keeping SA viscosity, more or less constant, influence of SA G/M ratio on drug release was studied. When SA was used as the matrix alone, no statistical difference was found between high G content SA and low G content SA based system ($f_2 > 50$), with more than 90% drug released in 4 h (Fig. 2a). In contrast, when combined with CS, the system achieved slow drug release for 24 h, with low G content SA containing system showing slower release (Fig. 2b), although no statistical difference between CS-SA with low G content and CS-SA with high G content groups were found ($f_2 > 50$).

In CS-SA combination system, influence of SA G/M ratio on tablets swelling and erosion behavior is shown in Fig. 2c and d. It was noted that the swelling percentage was SA G content related, higher swelling ratio was observed in low G content group compared to high G content group. As for the erosion percentage, no difference was observed in the first 12 h, thereafter, high G content group had higher erosion than that of low G content group. The thickness of PEC film formed on the tablet surface was measured, it was 1.79 ± 0.05 mm and 1.57 ± 0.07 mm for high G content (CS-SA (LFR5/60)) and low G content (CS-SA (LD)) system respectively. This study indicated that although low G content SA group (CS-SA(LD)) had a higher swelling ratio, due to the thicker PEC film of high G content group (CS-SA(LFR5/60)), as a compromise, drug release from CS-SA-based matrix tablets was almost unaffected by the G content of SA.

Influence of the SA Salt Type

Metal ions may affect drug release, swelling, and erosion in SA alone or CS-SA matrix tablets. Now that the above study demonstrated that G content had no considerable influence on drug release, here SA of different salt, sodium salt (LF200M), potassium salt (KF200M), magnesium salt (LFMg5/60), and calcium salt (PH1033) were selected in this study. As shown in Fig. 3a, when SA of different salt form was used as the matrix alone, diverse drug release behavior was observed. In contrast, when these SAs were combined with CS, stable and prolonged drug release profile up to 24 h was obtained (Fig. 3b), indicating drug release diversity due to SA structure difference can be well eradicated in CS-SA combination system, which is beneficial to the manufacture of constant quality products.

For the CS-SA matrix, influence of SA salt form on the swelling and erosion behavior is shown Fig. 3c and d. It was noted that potassium salt group had the highest swelling ratio followed by calcium salt, sodium salt, and with the least swelling observed for magnesium salt group. And the erosion was in the order calcium salt < sodium salt = magnesium salt < potassium salt. CS-SA potassium salt group presented the largest swelling ratio; meanwhile, the fastest erosion rate and CS-SA magnesium salt group system had the least swelling degree with erosion rate comparable to sodium salt group. PEC film formed on the tablets surface was also influenced by SA salt type, the thickness of PEC film formed with CS-SA(KF200M, K), CS-SA (LFMg5/60, Mg) , CS-SA (LF200M, Na), and CS-SA (PH1033, Ca) combination system were 2.00 ± 0.12 mm, 1.87 ± 0.09 mm, 1.45 ± 0.06 mm, and 1.70 ± 0.05

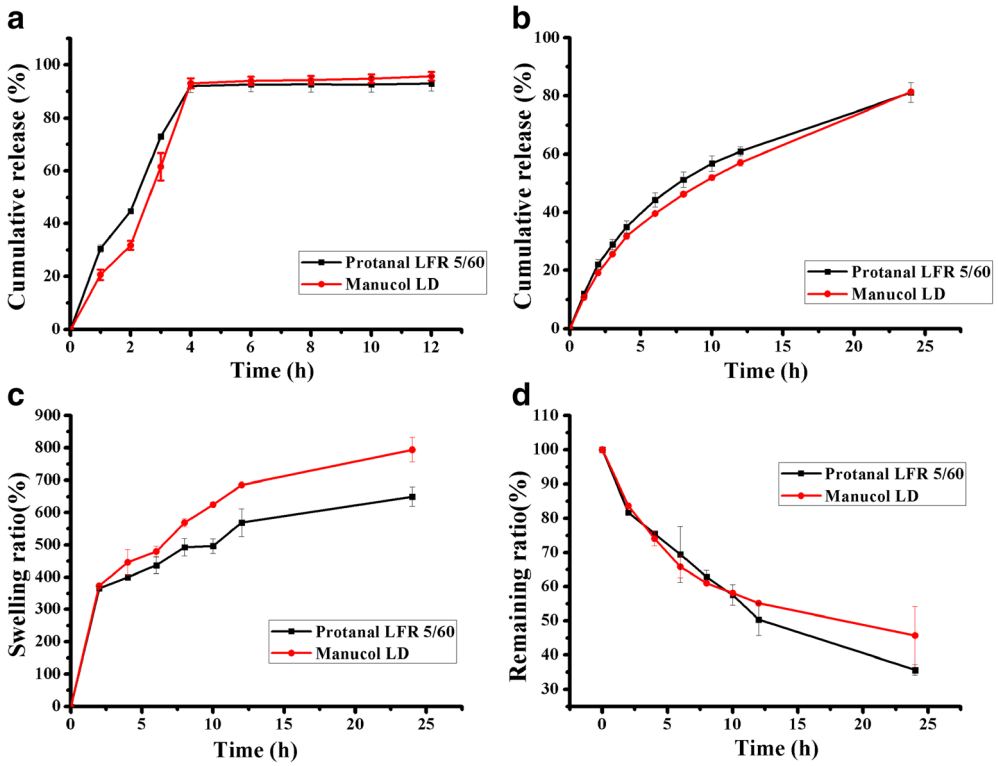

Fig. 2. Influence of SA G/M ratio on TH release from matrix tablets based on **a** SA and **b** CS-SA and swelling and erosion behavior of CS-SA (1:1) based tablets in SGF followed by SIF. **c** Swelling ratio and **d** remaining ratio

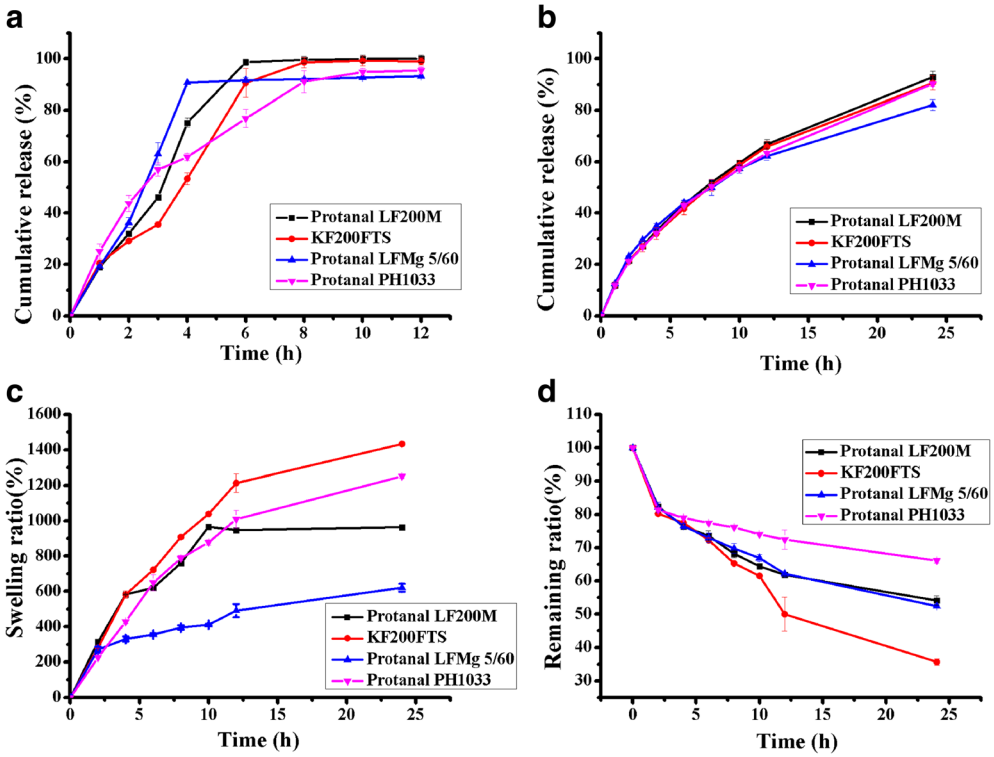

Fig. 3. Influence of the SA salt type on TH release from tablets based on **a** SA and **b** CS-SA, and swelling and erosion behavior of CS-SA (1:1) tablets in SGF followed by SIF. **c** Swelling ratio and **d** remaining ratio

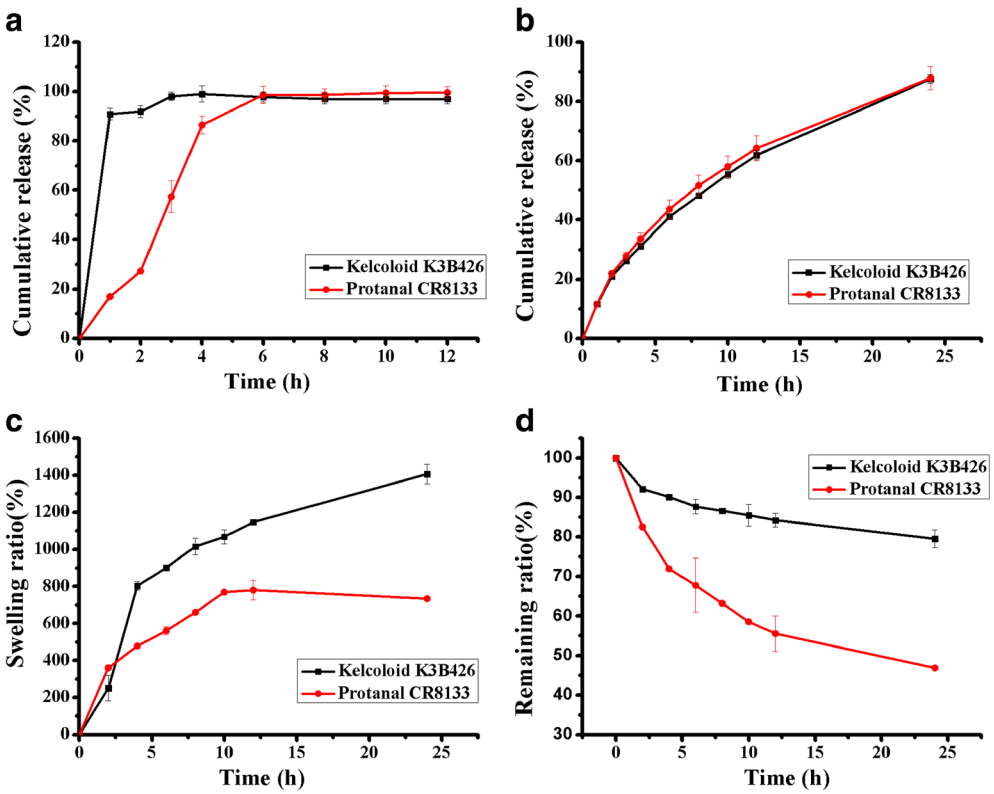

Fig. 4. Influence of the degree of esterification of alginate on TH release from tablets based on **a** SA and **b** CS-SA, and swelling and erosion behavior of CS-SA (1:1) matrix in SGF followed by SIF. **c** Swelling ratio and **d** remaining ratio

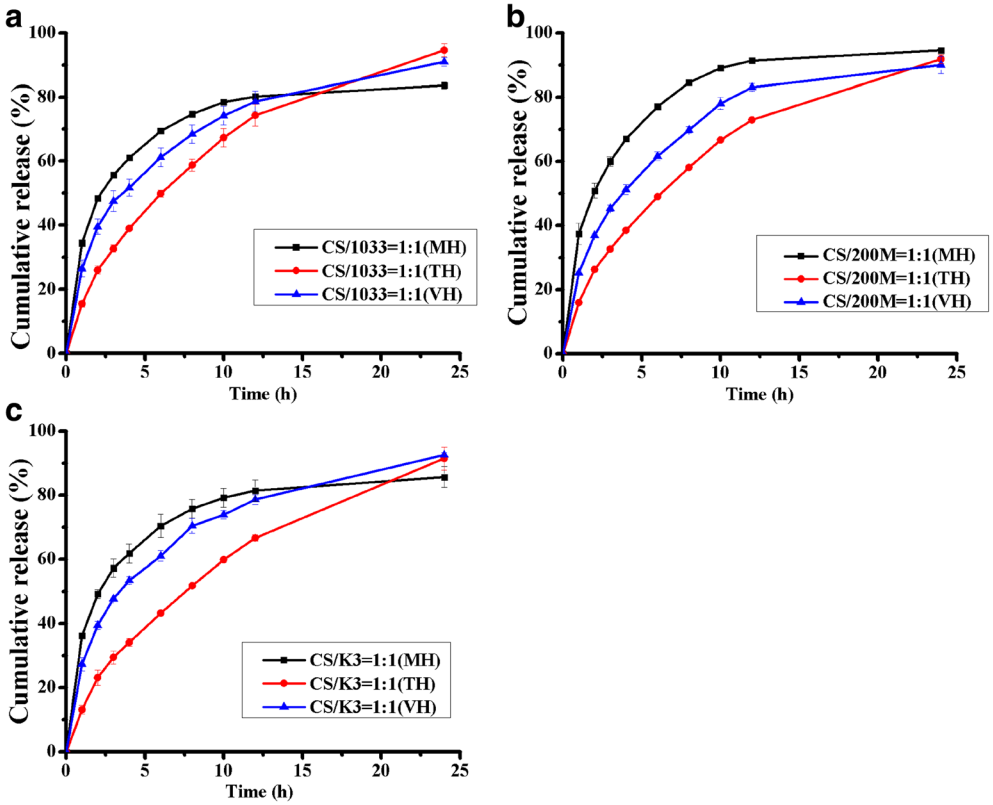

Fig. 5. Dissolutions profiles of different drugs based on CS-SA. **a** CS-SA (PH103)3; **b** CS-SA (LF200M), and **c** CS-SA (K3)

mm, respectively. This study indicated of potassium and magnesium salt of SA can help to form PEC of higher thickness.

Influence of Esterification of SA

Influence of SA esterification on drug release was investigated. While SA alone was used as a carrier, its degree of esterification had significant influence on drug release, and approximately 90% TH was released in 1 h when esterified SA was used. In contrast, slow drug release for up to 6 h was observed for non-esterified SA (see Fig. 4a). However, in CS-SA combination system, irrespective of SA type, it can achieve sustained drug release for 24 h (Fig. 4b) and there was no statistically significant difference between esterified and non-esterified SA containing group ($f_2 > 50$). This study indicated that esterification degree of SA had a great influence on drug release for a single SA system, but for CS-SA combination system, it had less effect on drug release.

For CS-SA combination tablets, influence of esterification of SA on the swelling and erosion behavior was studied. See in the Fig. 4c and d, esterified SA containing tablets had higher swellable ratio and lower erosion rate. And the esterified SA containing tablets still remained 79% of its initial weight at 24 h, which might be related to the much thicker film formed by CS-SA (K3B426). The film thicknesses of CS-SA matrix tablets were 2.82 ± 0.26 mm and 1.52 ± 0.05 mm for esterified SA (K3B426) and non-esterified SA (CR8133) containing systems, respectively. This study showed that esterified SA can help to form thicker PEC film, but its higher swelling capacity and lower erosion rate counteract its impact drug release.

Table II. Mathematic modeling and drug release kinetics based on tablets with CS/SA (1033)

Drug	k ($\%h^{-1}$)	$k_{1.2}$ ($\%h^{-1}$)	$k_{6.8}$ ($\%h^{-1}$)	Correlation coefficient (R)			*n*
				First-order	Higuchi	Peppas	
TH	3.94	13.03	4.82	0.9974	0.9945	0.9996	0.610
MH	3.48	24.24	3.16	0.9693	0.9104	0.9990	0.400
VH	3.79	19.74	3.92	0.9849	0.9720	0.9983	0.437

Influence of Drug Properties on CS-SA as Sustained Release Matrix

It is known that in addition to matrix properties, the nature of drug is also greatly affecting drug release behavior, including solubility and MW (21). Therefore, based on the above studies, with three representative SAs (K3, PH1033, LF200M), the applicability of CS-SA combination system on the release of drugs with different solubilities was explored. Three model drugs with different solubility were selected: slightly soluble theophylline (TH, 12 mg/mL in water, Mw 180.17), easily soluble metformin hydrochloride (MH, 346 mg/mL in water, Mw 165.63), and venlafaxine hydrochloride (VH, 558 mg/mL in water, Mw 313.87). The solubility of the three model drugs was pH independent.

As shown in Fig. 5, for TH and MH with similar molecular weight but different solubility, the release of TH can be well controlled for up to 12 h by CS-SA complex system despite of SA type, but the sustained release of MH was only maintained for around 12 h. Moreover, it was pointed out that with comparable solubility but different MW, the release of VH and MH was varied, slower release of VH was observed compared with that of MH. Therefore, the results indicated that the release of water-soluble drugs with small MW was not well controlled by CS-SA matrix tablets and slightly soluble drugs or water-soluble drugs with large molecular weight are good candidates.

Thereafter, taking CS-SA (CR1033) combination system as an example, drug release kinetics and release mechanism was investigated. As shown in Table II, the three drugs were released from the matrix according to first-order kinetics. Based on the results of Ritger-Peppas equation, TH was mainly released by the non-Fickian diffusion mechanism, it means that the erosion and diffusion mechanisms jointly controlled drug release ($0.45 < n < 0.89$), while water soluble larger VH and MH were mainly released by diffusion ($n < 0.45$).

CONCLUSIONS

This study indicated that when SA alone was used as a matrix, the SA properties, including the viscosity, G content, salt type, and esterification degree, had a great influence on drug release. The higher the viscosity of SA, G content, and degree of esterification, the faster the swelling and thus the slower the erosion of tablets. The salt type had a great influence on the dissolution and swelling. As noted, the swelling ratio of potassium salt was the highest and the dissolution was also the fastest. In contrast, when SA was combined with CS as a combination matrix, little effect of SA properties on drug release was observed, indicating drug release diversity due to SA structure difference can be well eradicated by CS-SA combination, which is beneficial to manufacture products of constant quality. Moreover, for CS-SA combination system, SA of low viscosity is beneficial in sustaining drug release. CS-SA matrix tablets are suitable to control the release of slightly soluble drugs or water-soluble drugs with large molecular weight.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest The authors declare that they have no conflict of interest

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