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Hydration, Erosion, and Release Behavior of Guar-Based Hydrophilic Matrix Tablets Containing Total Alkaloids of *Sophora alopecuroides*

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It is a challenge to deliver water-soluble drug based on hydrophilic matrix to colon because of swelling and erosion of polysaccharides in contact with media. In our study, guar-based hydrophilic matrix tablets containing water-soluble total alkaloids of *Sophora alopecuroides* prepared by wet granulation technique were evaluated. A novel method was established to investigate the changes of swelling and volume for guar-based tablets in undynamic state, which generally showed a rapid swelling and volume change in the first 9 h, then the hydrated speed slowed down. On the other hand, the influence of different pH of the media on water uptake and erosion of various guar-based formulations in dynamic state indicated that the hydrated constants in simulated gastric fluid (SGF) was higher than that in SIF, which followed varied mechanism of water penetration by fitting Davidson and Peppas model. The extent of erosion was between 22.4 and 32.6% in SIF within 360 min. In vitro sophoridine release studies in successive different mimicking media showed that the guar matrix tablets released 13.5–25.6% of sophoridine in the first 6 h; therefore it was necessary to develop the bilayer matrix tablet by direct-compressing coating 100 mg guar granula on core tablet. The initial release of coated tablet was retarded and the bilayer matrix tablet was suitable for colon target.

Keywords guar gum; swelling; hydration; erosion; drug release; hydrophilic matrix tablet; total alkaloids of *Sophora alopecuroides*

INTRODUCTION

Total alkaloids of *Sophora alopecuroides* are a mixture of extract from root or seed of *S. alopecuroides* L., Chinese medicine Ku-dou-zi, which have been used for gastrointestinal disorders in Chinese folk medicine for a long time (Xinli, Wubao, Hang, Alkber, & Li-xin, 2005). They are mainly made up of six active components—that is, sophoridine, sophocarpine, matrine, oxymatrine, sophoraramine, and aloperine—and have been widely used as an ingredient approved by Chinese SFDA for many years, which contain not less than 24% sophoridine and not less than 95% alkaloids, calculated reference as sophoridine (Song, Xu, Tian, & But, 1999). The pharmacological studies have shown that total alkaloids of *S. alopecuroides* have pleiotropic effects including anti-inflammation, antivirus, antitumor and immunomodulation, and so on (Han, Zhou, & Liu, 2006). Cheng et al. (2006) and Zheng, Niu, Liu, Shi, and Lu (2005) demonstrate the effectiveness of matrine and oxymatrine for colitis. Our recent work showed that total alkaloids of *S. alopecuroides* could yield protective effect against colitis in 2,4,6-trinitrobenzene sulfonic acid/ethanol-inducing rat via antioxidation (Jianguo & Hongzhu, 2006). Therefore, it is believed that total alkaloids of *S. alopecuroides* would be a promising candidate for colitis.

To target total alkaloids of *S. alopecuroides* to colon, biodegradable natural polysaccharides, which are degraded exclusively by colonic bacteria enzyme, are ideal carriers, compared with pH-dependent, time-dependent, and pressure-dependent materials (Fude et al., 2007; Kosaraju, 2005). Guar gum, one of the natural polysaccharides, has been extensively investigated for colon drug delivery in vitro and in vivo, such as 5-fluorouracil (Ji, Xu, Sun, Lu, & Wu, 2007a), indomethacin (Ji, Xu, & Wu, 2007b), metronidazole (Mundargi, Patil, Agnihotri, & Aminabhavi, 2007), methotrexate (Chaurasia et al., 2006), ibuprofen (Das, Wadhwa, & Srivastava, 2006), rofecoxib (Al-Saidan, Krishnaiah, Satyanarayana, & Rao, 2005), tinidazole (Krishnaiah, Muzib, Bhaskar, Satyanarayana, & Latha, 2003), celecoxib (Krishnaiah, Karthikeyan, & Satyanarayana, 2002), and so on. Guar-based matrix preparations containing different proportions show variable release in simulated gastric fluid (SGF), simulated intestine fluid (SIF), and simulated cecal fluid (SCF) within determined time. But one of the shortcomings of guar in targeting drug to colon is its solubility and swelling in physical gastrointestinal fluids, which cannot completely deliver all the loaded components to desiring sites. Herein, various measures have been taken to reduce guar swelling, erosion, such as coating ethylcellulose (Ji et al., 2007a), Eudragit-L100 (Ji et al., 2007b), phosphated crosslinked (Chaurasia et al., 2006), graft

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copolymer of methacrylic acid with guar (Mundargi et al., 2007), or direct compression of guar (Varshosaz, Tavakoli, & Kheirolahi, 2006). However, so far little has been known about the guar swelling and erosion in SGF and SIF.

The purpose of this study is to prepare total alkaloids of *S. alopecuroides* matrix tablet for colon targeting and delve its changes of swelling, volume, and erosion and release mechanism in different media. A novel method was established to investigate the changes of swelling and volume for guar-based tablets. The release of sophoridine in different types of physiologically relevant dissolution media was quantitated using high-performance liquid chromatography (HPLC). Our work showed that hydration velocities of total alkaloids of *S. alopecuroides* matrix tablets in SGF were higher than that in SIF; furthermore, the erosion percent in SIF at the speed of 150 rpm dissolution even reached to more than 30% within 6 h. Therefore, it is necessary to control the initial rapid release in SGF and SIF. The bilayer matrix tablet showed good site specificity according to the sophoridine release profiles.

MATERIALS AND METHODS

Materials

Total alkaloids of *S. alopecuroides* (98.2% total alkaloids, containing 43.8% sophoridine determined by HPLC) were purchased from YanChi Pharmaceutical company (Ningxia province, China). Guar gum (viscosity of 1% aqueous solution is 3,145 cps, particle size <150 mesh) was obtained from H. B. Gum Ind. Pvt. Ltd. (Kaloe [N.G.], Gujarat, India) Dextrin and soluble starch were of pharmaceutical grade and used as supply without further purification. Other reagents were of analytical grade.

Preparation of Guar-Based Matrix Tablets

Matrix tablets containing 100 mg of total alkaloids of *S. alopecuroides* were prepared by wet granulation/compression method using 20% (wt/vol) of soluble starch solution as binder. In detail, guar gum and dextrin were sieved through 80-mesh sieve, then the mixed powder was transferred to a mortar, and was thoroughly blended for 5 min. Total alkaloids of *S. alopecuroides* were dissolved in 20% (wt/vol) soluble starch solution as binder, and the determined amount of solution was added and the powder mixture was milled continuously to make paste. The homogeneous wet mass was forced through a 22-mesh sieve and dried at 80°C for 3 h. The dried granula were passed through a 20-mesh sieve. The uniformity of mixture was evaluated by conducting content uniformity test on samples of the granula. Magnesium stearate in 0.5% was added and mixed thoroughly with the granula. Then, the granula were compressed using 11 mm round and flat punches on a ZDY-8 Single-Pounch Rotary Tablet Press (Yuandong Pharmaceutical Machinery Co., Shanghai, China). The tablet formulations are given in Table 1. The process of all tablet batches was monitored for physical characteristics of granula and tablets, such as density of granulation, Carr's index, angle of repose, average particle size retain, weight of tablet, hardness, and friability.

TABLE 1
Unit Formula of the Prepared Tablets

Matrix Formulation	Alopecuroides Alkaloids (mg)	Guar Gum (mg)	Dextrin (mg)
A	100	100	150
B	100	125	125
C	100	150	100
D	100	175	75
E	100	200	50

Matrix Tablet Evaluations

Characterization of the Granula

Carr's Index. The bulk density of the granulation was determined by filling the granulation into a messcylinder to the 100-mL mark. The graduated messcylinder was weighed and the bulk density (V_B) calculated as the ratio of the sample weight to sample volume. The graduate was then tapped on a flat surface. The tap density (V_T) was calculated as the ratio of sample weight to the final sample volume after 100 taps. No further volume reduction occurred after 100 taps. The changes occurring in packing arrangement during the tapping procedure were expressed as the Carr's index (I) as shown by the following equation (Ebube et al., 1997). Each sample was tested for three times.

$$I = \left(1 - \frac{V_B}{V_T}\right). \quad (1)$$

Angle of Repose of the Granulation. Angle of repose was determined by the fixed funnel method (Krishnaiah, Satyanarayana, Dinesh Kumar, Karthikeyan, & Bhaskar, 2002). A funnel with the end of the stem cut perpendicular to the axis of symmetry was secured with its tip at a given height (H) above a graph paper placed on a flat horizontal surface. The granulation was carefully poured through the funnel until the apex of the conical pile so formed just touched the tip of the funnel. The mean diameter ($2R$) of the base of the powder cone was determined and the tangent of the angle of repose was given by $\tan \alpha = H/R$, where α was the angle of repose.

Average Particle Size Retention. Particle size distribution of each batch was determined by sieve analysis using 100 g of the test granulation and a series of Chinese standard sieve ranging in size from 20 mesh to 60 mesh. The test granulation was placed on the top sieve and mechanically shaken for 3 min on a shaker. Keep the sieve horizontal during the test. The fraction retained on each screen was finely weighed and its weight percent was calculated.

Tablet Weight Variation Testing

Twenty matrix tablets were randomly selected and accurately weighed on an analytical balance (Sartorius CP324S, Goettingen, Germany). The results were expressed as mean values and standard deviation of 20 determinations.

Hardness and Friability Determination

Twenty matrix tablets were sampled and individually subjected to test for hardness using Hardness Tester for Tablets (Tianda Tianfa, pharmaceutical testing instrument manufacturer, Tianjin, China). The tablet hardness was expressed in kilogram unit. The mean values and standard deviation of the tablet hardness were calculated. Tablet friability test was performed on finely weighed 10 tablets at 25 rpm for 5 min using FT-2000S Friability Tester (Tianda Tianfa, Tianjin, China). Three replicate determinations of each formulation were averaged.

Swelling and Erosion Studies

Swelling and Volume Change in Undynamic State

The swelling and volume changes were studied, which occurred in the structure of the matrix when it came into contact with water. Put the finely weighed matrix tablets into 100 mL weighed volumetric flask. Then, add distilled water (25°C) into the volumetric flasks using burette (precision to 0.1 mL), and read the volume of water. At the predetermined time, decant the distilled water carefully, weigh the volumetric flasks (keep the swelling tablets in the flasks) using an analytical balance (Sartorius CP324S), and then determine the amount of distilled water (25°C) that was added to the volumetric flask and calculate the change of water volume and wet tablet weight. Repeat the above procedure at the predetermined time. The weight and volume changes could be accurately measured. In the course of this test, keep the samples still. For this study, the changes of sample were recorded every 4 h for 72 h. Each sample was tested for three times.

Swelling and Erosion Change in Dynamic State

Measurement of swelling and erosion rates of guar-based matrix tablets was performed in the 900 mL of release medium at 37 ± 0.5°C and a rotation speed of 150 rpm according to Chinese Pharmacopoeia (2005 ED) paddle method. Weighed tablets (w_0) were placed in the dissolution medium of 0.1 M HCl (pH 1.2) or phosphate sodium buffer (pH 6.8). After predetermined time, the tablets were withdrawn from the medium and carefully blotted to remove excess water and then weighed (w_1) on an analytical balance (Sartorius CP324S). The wet samples were then dried in an oven at 80°C for 24 h, allowed to cool in a desiccator and finally weighed until constant weight was achieved (final dry weight, w_2). The test was performed in triplicate for each time point, and fresh samples were used for each individual time point (Sriamornsak, Thirawong, & Korkerd, 2007).

The percentage of weight changes because of the absorbed liquid or water uptake and the percentage of the remaining tablets after erosion (ES) were estimated at each time point from following equations:

$$\%\text{Weight change} = \frac{w_1 - w_0}{w_0} \times 100 \tag{2}$$

$$\%\text{Remaining} = 100 - \text{ES}, \tag{3}$$

where ES was calculated from the following equation:

$$\text{ES} = \frac{w_0 - w_2}{w_0} \times 100. \tag{4}$$

Determination of Sophoridine in Tablet Formulations

Content of sophoridine (its chemical structure is shown in Figure 1) in tablets and release media was determined by a reported HPLC method (criterion of total alkaloids of *S. alopecuroides* approved by Chinese SFDA: WS-10001-(HD-1391)-2) with slight modification. The Agilent 1100 series HPLC system consisted of a quaternary pump, a degasser, an autosampler, a column heater, and a tunable wavelength UV detector. The separation was performed at 30°C using a Kromasil 100-5C column (4.6 mm × 250 mm). The mobile phase was a mixture of acetonitrile, 0.02 mol KH_2PO_4 solution at the ratio of 69:31 (vol : vol, pH 6.0), pumped at a flow rate of 1.0 mL/min. Detection wavelength was 205 nm. Good linearity was observed in the range of 0.02–8.3 μg with a high correlation coefficient ($y = 3460.5x + 15.521$, $r = 1$). Retention time under present HPLC conditions was 4.236 min, as shown in Figure 2. Specific standard curve was constructed for the estimation of sophoridine in release media.

In vitro Drug Release Studies

Drug release studies were carried out based on Chinese Pharmacopoeia (2005 ED) paddle method in the 200 mL release medium at 37 ± 0.5°C and a rotation speed of 50 rpm.

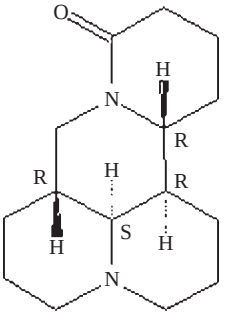

FIGURE 1. The chemical structure of sophoridine.

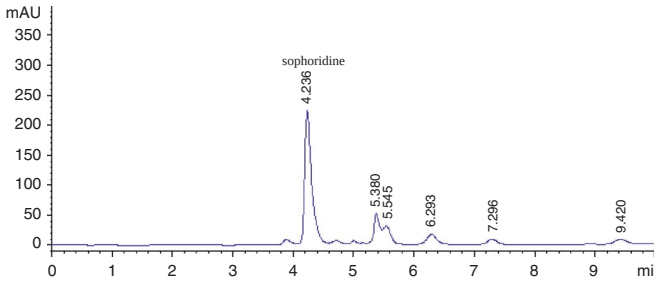

FIGURE 2. Chromatogram of total alkaloids of *Sophora alopecuroides.*

Dissolution rate test was performed in 0.1 M HCl solution for 2 h. Then the dissolution medium was replaced with pH 6.8 phosphate sodium buffer and tested for drug release for 4 h. After completing this, the swollen matrix tablets were immersed in the 4% (wt/vol) rat cecal content and pH 6.8 phosphate sodium buffer for the predetermined time. As the caecum is naturally anaerobic, the experiment was carried out with continuous CO_2 supply into media. At different time intervals, 1 mL of the dissolution sample was filtered with 0.2-μm membrane filter and replaced with 1 mL of fresh rat cecal content phosphate sodium buffer bubbled with CO_2. Rat cecal content medium was prepared according to the previous method (Al-Saidan et al., 2005). Three samples for each data points were analyzed for sophoridine content.

RESULTS AND DISCUSSION

Physical Properties of Guar-Based Matrix Tablets

The comparison of physical properties of the matrix tablets containing different amounts of guar is shown in Table 2. These results indicated that the granulations of various formulations showed good flow characteristics, hence, good compressibility. The granulation of formulation A was more fragile; with the increase of the amount of guar gum, the granulations of formulations B–D became less fragile. The sieve analysis data for granulations showed a shift in particle size distribution from 5.2 to 15.2% because of higher stickiness of wet mass with more amount of guar. All tablets prepared in this study met the requirement of the Chinese Pharmacopoeia (2005 ED) for weight variation tolerance. The hardness and friability of different tablet formulations ranged from 3.8 to 5.1 kg and from 0.53 to 0.88%, respectively. At compression force of 25 kN, the hardness of formulation C was maximal, probably because of the better proportion of the fine fraction and coarse fraction of the granula, whereas the friability of formulation E was 0.88%, and there was more coarse fraction of the granula leading to a decreasing bonding force and less flexibility in granulations compressing.

Swelling and Erosion Behavior of Guar-Based Matrix Tablets

Influence of the Distilled Water Medium on Water Uptake and Volume Change in Undynamic State

Guar gum is easy to get hydrated and forms a viscous gel layer that slows down further seeping-in of dissolution fluids toward the core of matrix tablet. To verify the effect of water on swelling and volume, five different formulation tablets were compared. The results of variable volume and of weight gain of swelled matrix were shown in Figure 3. The swelling behavior indicated that these matrix generally showed a higher ability of swelling in first 9 h and then the hydrated speed slowed down and got balanced after 72 h. Volume variations of five formulations ranged from 1.7 to 2.7 mL, the constants were between 0.0004 and 0.0008 mL/h, increasing with higher amount of guar. Water uptake rate varied with the amount of guar, and percent weight gain was approximately at a range of 1,264–1,429%, hydrated constants between 0.0004 and 0.0008 g/h. In undynamic state, swelling for guar matrix tablets was the main phenomenon, and its rate of hydration was related to the amount of the hydroxyl groups. The experiments indicated that there was a fast swelling phase once the tablets contacted the media, with the gel barrier formation following a slow swelling phase. Volume variations became obvious with the increase of guar proportion.

Influence of pH of the Media on Water Uptake and Erosion

The swelling and erosion studies were carried out in various guar formulations. The results of these tests in SGF and SIF were provided as the percentage of weight changes and percentage of the remaining tablet mass, as shown in Figure 4. The swelling behavior indicated a rate at which these formulations absorbed water from dissolution media and swelled. These matrix generally showed a higher ability of swelling in SGF than that in SIF, in which the hydrated constant was ranged from 0.0018 to 0.0031 g/min within 120 min in SGF and from 0.0008 to 0.0014 g/min in SIF within 360 min. Changes of pH from 6.8 to 1.2 resulted in different hydrated constant, probably because of the easier phosphated crosslinking of guar in SIF than that in SGF, and beta 1–4 glycosidic linkages in chemical structure of guar gum might be hydrolyzed in pH ≤ 3 medium circumstance. The percentage of the remainings of the matrix is also shown in Figure 4, and it reflected the erosion of matrix during the dissolution process. Weight loss from the tablets increased progressively with the erosion time. The extent of erosion was between 1.5 and 6.1% in acidic conditions within 120 min, between 22.4 and 32.6% in phosphate sodium buffer within 360 min, in which guar : dextrin ratio was profoundly affected by the polymer relaxation dissolution. As the guar : dextrin ratio increased, the hydrated matrix would be less porous with a high degree of tortuosity leading to high gel strength, slow erosion, and slow swelling. Therefore, it is pivotal to control the erosion to target total alkaloids of *S. alopecuroides* to colon.

TABLE 2
Physical Characteristics of Matrix Tablets for Various Formulations

Matrix Formulation	Density of Granulation (g/mL)		Carr's Index (*I*)	Angle of Repose (°) (*n*=3)	Average Particle Size Retain %			Hardness (kg) (*n*=20)	Friability (%) (*n*=3)	Tablet Weight (g) (*n*=20)	Drug Content (%) (*n*=3)
	V_B	V_T			(20 mesh)	(20/40 mesh)	(40/60 mesh)				
A	0.48	0.56	14.3	28 (2.8)	5.2	34.3	40.4	3.8 (0.02)	0.61 (0.05)	0.348 (0.006)	98.68 (3.637)
B	0.49	0.55	14.0	25 (2.1)	5.7	32.2	38.1	4.3 (0.03)	0.82 (0.05)	0.354 (0.008)	101.33 (2.740)
C	0.50	0.55	9.0	25 (3.5)	8.3	36.7	39.2	5.1 (0.09)	0.53 (0.03)	0.352 (0.007)	99.68 (0.915)
D	0.51	0.55	8.9	25 (3.8)	12.3	35.3	38.3	4.3 (0.24)	0.76 (0.12)	0.351 (0.007)	98.35 (1.655)
E	0.50	0.54	10.7	26 (3.7)	15.2	36.2	38.5	4.3 (0.38)	0.88 (0.04)	0.349 (0.007)	98.21 (3.878)
Coated C								4.5 (0.045)	0.92 (0.04)		

Result represent means of replicate determinations with the standard deviation in parenthesis.

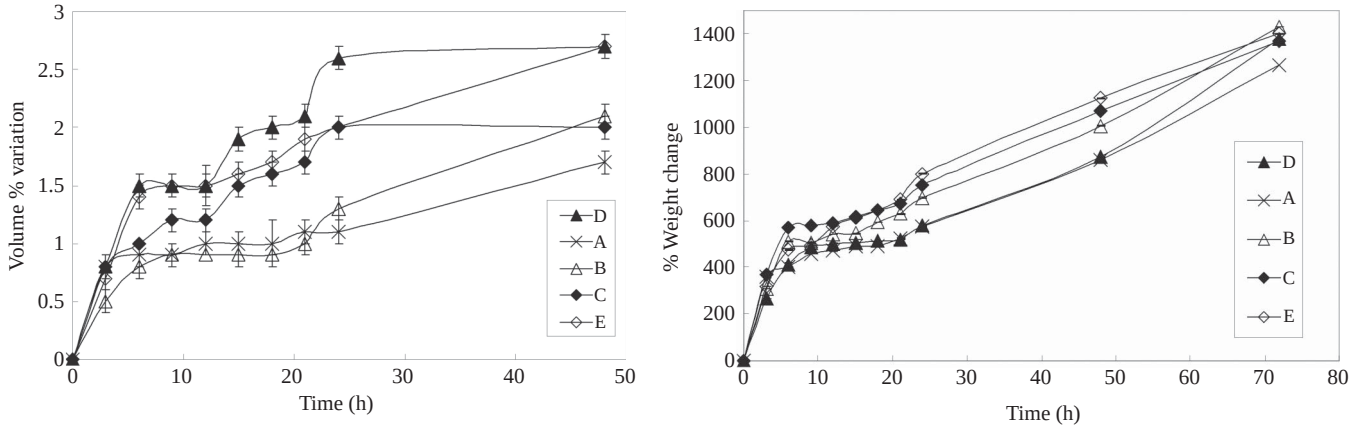

FIGURE 3. Percent weight gain (water uptake) and volume change of different guar-based formulations during the swelling study in undynamic state ($n = 3$).

To better understand the kinetics of the water uptake into hydrophilic matrix, the Davidson and Peppas mode is introduced (Fuertes, Miranda, Millan, & Caraballo, 2006).

$$W = k_s t^n, \quad (5)$$

where W is the weight gain of the swelled matrix, k_s is the kinetics constant of water penetration, t is the penetration time, and n is the exponent that depends on the water uptake mechanism. The swelling of the polymer depends on the rate of penetration of fluid into the matrix. The water uptake data were subjected to the Davidson and Peppas model to calculate the rate of water penetration. The results are shown in Table 3. According to the value of n, the water uptake of the guar matrix tablets in SGF followed a Fickian diffusion-controlled mechanism, $n < 0.5$. On the other hand, $n \geq 0.5$ in SIF, the mechanism of water uptake followed non-Fickian diffusion in which the rate of diffusion of liquids was equivalent to the rate of relaxation of the polymer.

In Vitro Drug Release Studies in Successive Different Mimicking Media

The matrix tablets were subjected to in vitro drug release studies in 0.1 M HCl (SGF, 2 h), pH 6.8 phosphate buffer (SIF, 4 h), and SCF, which contained 4% (wt/vol) rat cecal content after 7 days of 1% guar induction (Al-Saidan et al., 2005). The release results were shown in Figure 5. The guar-based matrix tablets released 13.5–25.6% of sophoridine in the first 6 h. Formulations A and B released 25.6 and 24.3% sophoridine, in the first 6 h and finally 98.69 and 99.35% within 10 h, respectively. Formulations D and E released 14.6 and 13.5% sophoridine in the first 6 h and released 99.67 and 98.96% at the end of 11 h of dissolution test, respectively, showing a slight lagged release behavior. Formulation C released 18.3% within 6 h, yet released 98.69% in SCF within 10 h. While the guar matrix tablets were immersed in the media, dextrin and soluble starch were preferentially dissolved; total diffusion of water-soluble alkaloids of *S. alopecuroides* was expected to take place through a porous network of guar matrix by capillary action, involved in the gel barrier and erosion. As the surface area of our matrix tablets was about 2.72 cm^2/tablet, the drug diffusion on the surface of the matrix tablet would aggravate an initial burst release together with the initial rapid swelling phase.

As we know that stomach and small intestine transit empty time is about 6 h, it is necessary to reduce the initial release of sophoridine to minimum in physiological environment of upper gastrointestinal tract.

To precisely target total alkaloids of *S. alopecuroides* to colon, we designed the bilayer matrix tablet by direct compressing coating of 100 mg guar granula on formulation C tablet because of their better physical properties. Guar granula (50 mg) was placed in the cavity by carefully centering the core tablet, then, addition of the remainder of coat weight was placed over the core. The coating material was compressed around the core tablet using 11 mm round concave punches by a single station tableting machine, slightly compressed for uniform spreading. Then, its physical properties and release were evaluated by the above methods, data are shown in Table 2 and Figure 5.

Bilayer matrix tablet met the required physical properties, its initial release was lagging. Within the first 6 h, there was only 6.78% drug released from matrix tablet, and almost no drug released within the 2 h, and the guar matrix completely dissolved in 10 h. The retardant layer could bypass the SGF release and followed a slow release of sophoridine in SIF; then with the guar degradation by colonic bacteria enzyme, sophoridine was released rapidly.

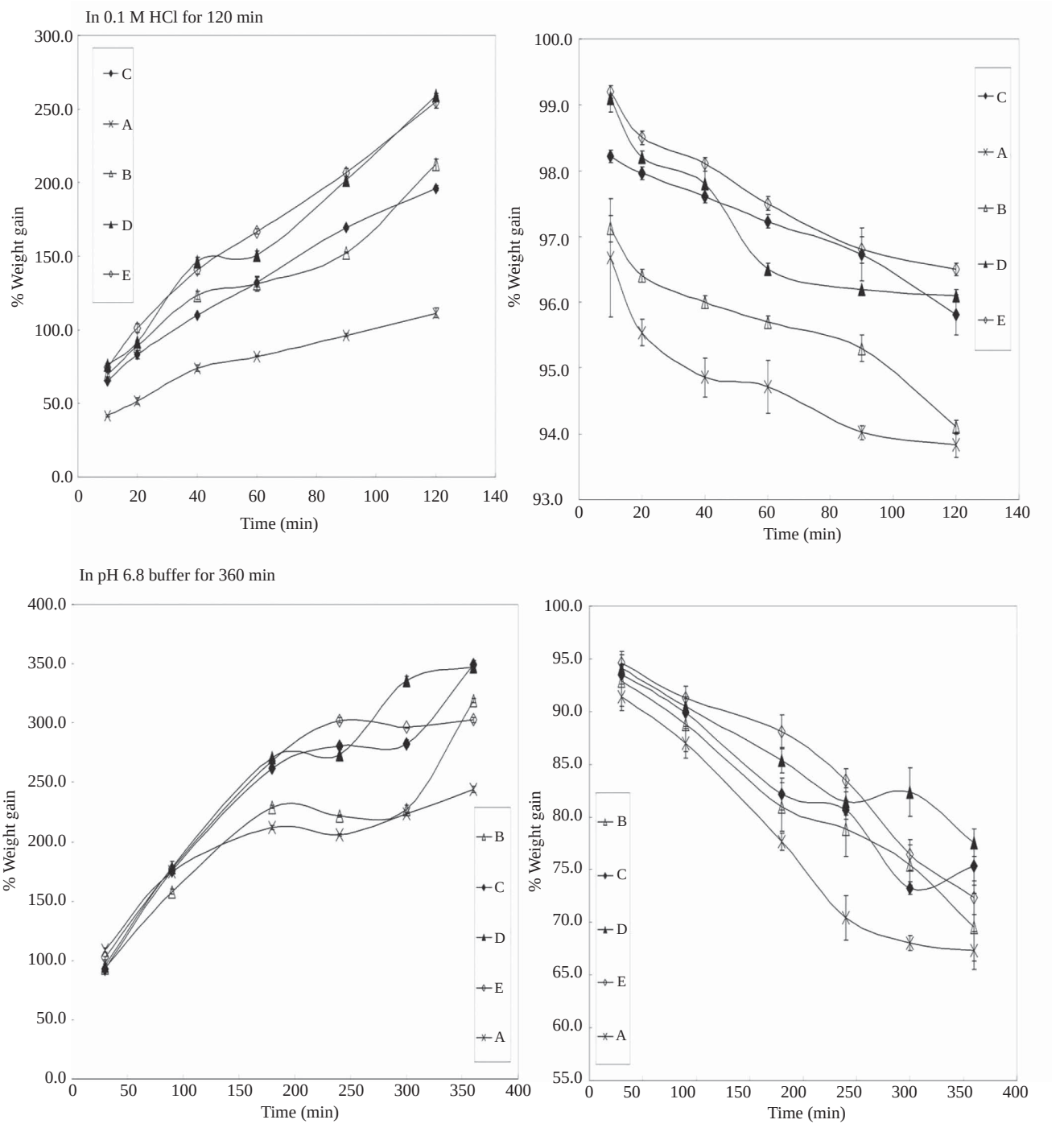

FIGURE 4. Percent weight gain (water uptake) and percent remaining of different guar-based formulations in 0.1 M HCl and pH 6.8 phosphate buffer (n=3) during the swelling study in dynamic state.

CONCLUSIONS

Guar gum, a natural nonionic polysaccharide, has various physiological actions, especially for colitis prevention (Naito et al., 2006), which has been wildly used for colon site drug carrier. As we know, developing oral tablets targeting the colon for water-soluble drugs has always been a challenge to the pharmaceutical technologist. In our work, we compared the difference of swelling and erosion for guar-based matrix tablets in two states: undynamic and dynamic. It was critical to control the release of water-soluble drug for colon site in the

TABLE 3
Kinetics Parameters of Water Penetration Based on the Davidson and Peppas Model for all the Matrix Formulations Studied

Matrix Formulation	*Ks*	*n*	r^2
In SGF			
A	–3.0012	0.3905	.9983
B	–3.0356	0.4225	.9794
C	–2.9873	0.4398	.9835
D	–2.0796	0.2317	.9607
E	–2.9641	0.4678	.9884
In SIF			
A	–2.5072	0.5225	.9483
B	–3.3791	0.4916	.9996
C	–3.4441	0.5334	.9858
D	–3.3157	0.518	.9847
E	–2.9326	0.5492	.9759

ks (% min^{-n}) is the kinetics constant of water penetration; *n* is the exponent that depends on the water uptake mechanism.

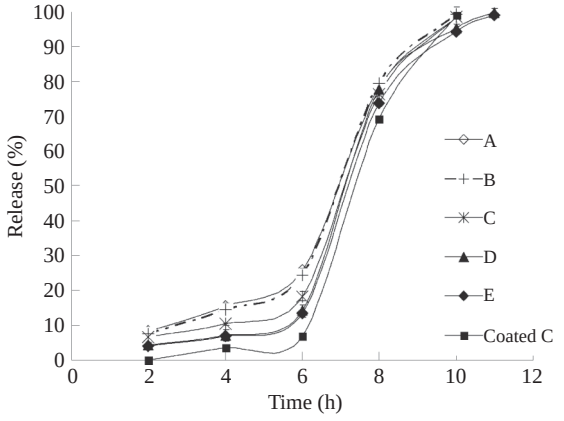

FIGURE 5. Release profiles of alopecuroides alkaloids from different guar-based formulations in SGF (2 h), SIF (4 h), and SCF (*n*=3), plotted as a function of time.

initial rapid swelling phase. Our study showed that it was effective to control its burst release by coating the retardant layer, certain amount of direct compression guar. However, extensive studies for in vivo release profiles of total alkaloids of *S. alopecuroides* are needed. As total alkaloids of *S. alopecuroides* are multiple components of mixture, the study on release of sophoridine did not elucidate other alkaloids releases owing to different physical chemistry properties. The following studies focus on the work of the synchronized releases and their inter-reactions of alkaloids.

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