Department of Pharmacy[1], Fuzhou General Hospital of Nanjing Military Region, Fuzhou, School of Pharmacy[2], Shenyang Pharmaceutical University, Shenyang, China

Preparation of the traditional Chinese medicine compound recipe Shuxiong sustained-release capsules by multiparticulate time-controlled explosion technology

HONG-TAO SONG[1], QIAN ZHANG[2], HUI-JUAN WANG[1], XIN-JIN GUO[1], DA-WEI CHEN[2], ZHONG-GUI HE[2]

Received May 26, 2006; accepted June 9, 2006

Dr. Hong-tao Song, Department of Pharmacy, Fuzhou General Hospital of Nanjing Military Region, Fuzhou 350025, China
sohoto@sohu.com

Pharmazie 62: 372–377 (2007) *doi: 10.1691/ph.2007.5.6097*

In this study the traditional Chinese medicine compound recipe (TCMCR) Shuxiong sustained-release capsules (SXSRC) were prepared by multiparticulate time-controlled explosion technology. First, Shuxiong pellets were prepared with the refined medicinal materials containing in the recipe of Shuxiong tablets. Then, the pellets were coated sequentially with an inner swelling layer containing low-substituted hydroxypropylcellulose as the swelling agent and an outer rupturable layer of ethylcellulose. Finally, SXSRC were developed by encapsulating five kinds of pellets whose respective coating level of outer layer was 0%, 9%, 15%, 18% and 20% at equivalent ratio in hard gelatin capsules. Under the simulated gastrointestinal pH conditions, the *in vitro* release test of SXSRC was carried out. The value of similarity factor (f_2) of hydroxysafflor yellow A and *Panax notoginseng* saponins, hydroxysafflor yellow A and ferulic acid, *Panax notoginseng* saponins and ferulic acid was 90.1, 77.3, 87.0, respectively. The release profiles of these three compositions from SXSRC showed a characteristic of obvious sustained-release and no significant difference between them. The results indicated that using multiparticulate time-controlled explosion technology various components in TCMCR with vastly different physicochemical properties could be released synchronously while sustained-releasing. That complies with the organic whole conception of compound compatibility of TCMCR.

1. Introduction

Traditional Chinese medicine compound recipe (TCMCR) is precious heritage of Chinese medicine and has made a prominent contribution to the prosperity of the Chinese nation. Now they are increasingly being understood and accepted by more and more people in the world. In recent years, quite great progress has been made in the dosage forms of TCMCR. However, the sustained or controlled release formulations of TCMCR shows considerable differences in quality and quantity compared with preparations of chemical medicine. In the previous studies some oral solid sustained-release preparations of TCMCR were prepared to control their diffusion or dissolution rates through the barrier of the systems and surrounding media such as film-controlling delivery systems (Wei et al. 2003; Li et al. 2004) and matrix-type delivery systems (Qiu et al. 2005). Systems floating in the stomach were also developed as sustained-release formulation of TCMCR (Liu et al. 2001). However, ingredients in TCMCR are considerably numerous and have vastly different physicochemical properties. In such delivery systems the release rates of hydrophilic ingredients were certainly faster than those of lipophilic ingredients. It is quite difficult to ensure that every component of TCMCR releases synchronously while sustained-releasing. However, according to the fundamental theory of traditional Chinese medicine separation of any active composition from TCMCR will make the ingredients fail to cooperate and supplement with each other and thus affect therapeutic efficacy.

To overcome this problem the pH-dependent multiparticulate site-specific release technology was attempted to develop a sustained-release formulation of TCMCR (Song et al. 2002, 2005). Drug release from this system relied on the variation of pH values at different places of the human gastrointestinal (GI) tract, independent of the physicochemical properties of the components containing in TCMCR. However, the transit time in human GI tract, especially the gastric emptying time of individuals varied remarkably and the transit time in the duodenum was very short, so there were great limitations in this technology. In this study, multiparticulate time-controlled explosion technology (Ueda et al. 1994a, 1994b) was applied to prepare a sustained-release formulation of TCMCR. The multiparticulate dosage form consists of a multiplicity of small discrete units, each exhibiting some desired characteristics. Together, these characteristic units provide the overall desired controlled release of the formulation. The time-controlled explosion system is made up of a drug-containing core, covered by a swelling layer and an outer rupturable

membrane (Song et al. 2003; Sungthongjeen et al. 2004). The expansion can be caused by effervescent excipients (Krögel and Bodmeier 1999) or swelling agents (Bussemer et al. 2003; Morita et al. 2000). The lag time can be precisely programmed by changing the outer membrane thickness (Ueda et al. 1994c). In this system, rupturing of the outer barrier is induced by the inner swelling layer upon water penetration through the outer membrane, and then the rapid release of every component containing in drug layer is initiated at the same time by destruction of outer membrane, independent of the physicochemical property of every component in itself.

In this study Shuxiong tablet (SXT) was selected as the model drug. It consists of root of *Panax notoginseng*, flower of *Carthamus tinctorius* and rhizoma of *Ligusticum chuanxiong*, which can produce reliable clinical effects on activating blood circulation, removing stasis and receiving pain. They are primarily applied to the treatment of chest distress, angina pectoris and myocardial infarction caused by coronary heart disease (Chinese Pharmacopoeia Commission 2005). At first each medicinal material containing in SXT was refined to prepare the sustained-release formulation, and Shuxiong pellets were prepared subsequently in a centrifugal granulator with the refined medicinal materials. Then, the core pellets were coated with two consecutive layers, an inner swelling layer and an outer rupturable membrane, respectively. Low-substituted hydroxypropyl cellulose (L-HPC) was selected as the swelling agent because of its superior swelling behavior and ethylcellulose (EC) was chosen as the outer coating material because it could form a mechanically weak and semipermeable film, which could rupture easily upon exposure to the dissolution medium and the resultant internal swelling pressure. Finally, five kinds of pellets with different release patterns were prepared by regulating the coating level and these characteristic pellets were filled together into capsules as the final dosage forms.

2. Investigations and results

2.1. Effect of the types of swelling agent on drug release

When the swelling and rupturable layers were both kept at 18% coating level, and the concentrations of hydroxypropyl methylcellulose (HPMC) and sodium dodecyl sulphate (SDS) in the inner coating solution were fixed, different coated pellets were prepared by taking L-HPC, carboxymethyl starch sodium (CMS-Na), polyvinylpolypyrrolidone (PVPP), croscarmellose sodium (CC-Na) and carboxymethylcellulose calcium (CMC-Ca) (3%, w/w) as the inner swelling agent, respectively. The dissolution tests were carried out by selecting hydroxysafflor yellow A as the measuring index. Fig. 1 shows that L-HPC and CMS-Na had strong swelling ability, while the swelling ability of PVPP, CC-Na and CMC-Ca was weak. Furthermore, only the coated pellets with L-HPC as the inner swelling agent could exhibit a characteristic burst release after a certain lag time, and a large amount of EC film could be observed floating on the dissolution medium. It could be concluded that with the penetration of water and the subsequent volume expansion of L-HPC, the resultant internal pressure got so strong that it caused the rupturing of the EC coating. The drug was then released rapidly due to the strong rupturing of the coating. In contrast, the release profile of drug from the coated pellets with CMS-Na as swelling agent was similar to the sustained release profile, but not the time-controlled release profile, and EC film

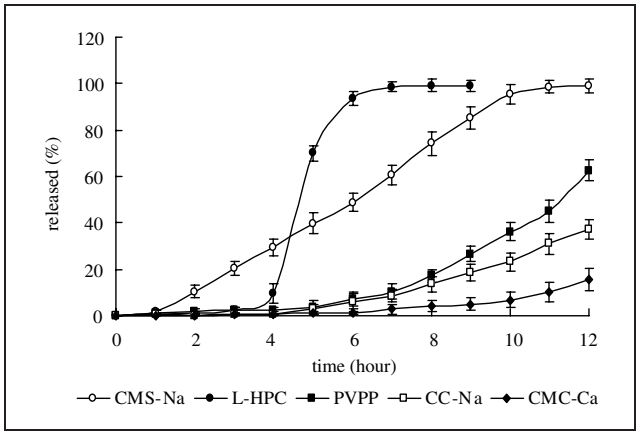

Fig. 1: Effect of the types of swelling agent on the release profiles

was not seen floating on the dissolution medium. The reason was possibly as follows: the penetrating water made the CMS-Na expand gradually and drug began to diffuse through the porous EC membrane. However, the internal swelling pressure produced by CMS-Na was not strong enough to break the EC coating, hence burst release could not be obtained all the time. The release mechanism of drug from the coated pellets with CMS-Na as swelling agent was equivalent to that of film-controlling delivery systems, and in such coated pellets the release rates of hydrophilic components were certainly faster than those of lipophilic components. Therefore, L-HPC was selected as the inner swelling agent for further studies.

2.2. Effect of SDS concentration in the coating solution of swelling layer on drug release

Keeping the respective concentration of L-HPC and HPMC in the coating solution of swelling layer as 3% and 1%, and holding the swelling and rupturable layers both at 18% coating level, the concentration of SDS in the inner coating solution was changed from 0%, 1.0%, 1.5% to 1.75%. Different coated pellets were prepared according to the above conditions and the corresponding release profile was measured by a pharmatest tester. The results (Fig. 2) demonstrated that within 9 h almost no drug release was observed from the coated pellets without the addition of SDS in the inner coating solution. When SDS concentration was 1.0%, the coated pellets showed almost no drug release within 5 h and after 5 h the release profile did not exhibit the burst release expected. The reason was probably that the low concentration of SDS made the penetrating rate of water so slow that the swelling agent could not fully expand within the desired time and consequently the EC film could not rupture. The penetrating water reached the core pellets and dissolved the drug, and then the dissolved drug diffused into the dissolution medium through the EC membrane. When the concentration of SDS was up to 1.5%, the coated pellets began to release drug after a lag time of 4 h and the accumulated release percentage was over 80% for the next 1.5 h, and the EC film could be found to break completely. When the concentration of SDS reached 1.75%, the coated pellets began to release drug after a lag time of 2.5 h and the accumulated release percentage exceeded 80% for the next 1.5 h. These results indicated that SDS concentration in the inner coating solution had an obvious effect on the delayed-release time of drug from the coated pellets, but did almost not affect the release rate after the lag time. It

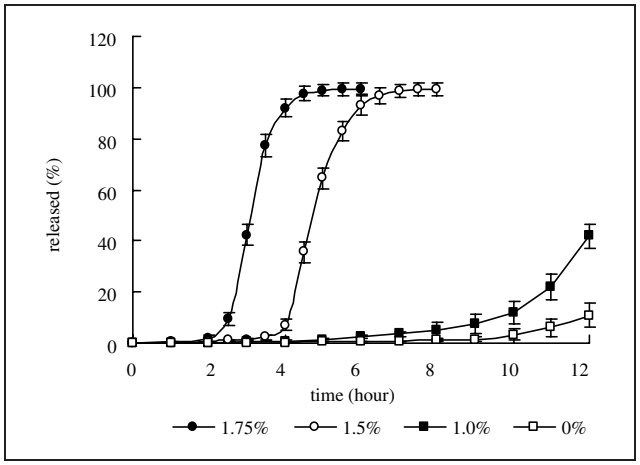

Fig. 2: Effect of the concentration of SDS in the swelling layer on the release profiles

could be inferred that with the increase of SDS concentration the penetrating rate of water gradually increased, and the inner swelling pressure could reach and exceed the critical swelling pressure more rapidly which was necessary to break the EC coating with certain thickness. Finally, the swelling pressure if high enough caused the rupturing of EC coating, at the same time the drug was released promptly within a short period due to the strong rupturing of the coating.

2.3. Effect of the coating level of swelling layer on drug release

Keeping the concentration of L-HPC, HPMC and SDS in the coating solution of swelling layer as 3%, 1% and 1.5% respectively, and remaining the rupturable layer at 18% coating level, the coating level of swelling layer was changed from 14%, 18% to 22%. Different coated pellets were prepared according to the above conditions and the corresponding release profile was measured by a pharmatest tester. The results (Fig. 3) show that the time-controlled burst release could be obtained only when the thickness of the swelling layer was up to certain level. When the swelling layer was at 14% coating load, the coated pellets began to release drug after a lag time of about 4.5 h and within the next 2.5 h the accumulated release percentage was just beyond 80%. In contrast, the accumulated release percentage of drug within 1.5 h after

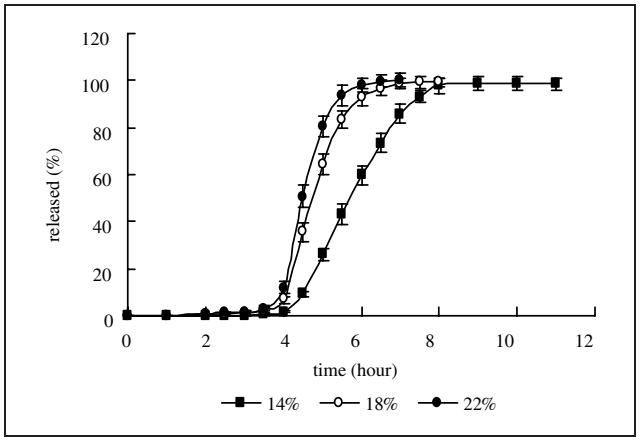

Fig. 3: Effect of the coating level of the swelling layer on the release profiles

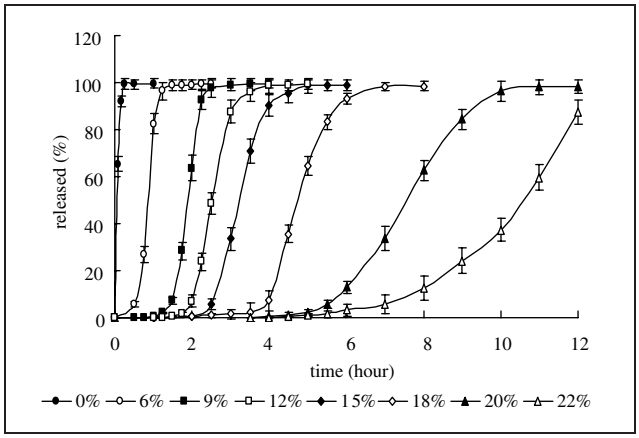

Fig. 4: Effect of the coating level of the rupturable layer on the release profiles

a lag time of 4 h from pellets at 18% and 22% coating load of swelling layer was over 80% and 90%, respectively.

2.4. Effect of the coating level of rupturable layer on drug release

When the swelling layer was kept at 18% coating level, the coating level of rupturable layer was varied from 0%, 6%, 9%, 12%, 15%, 18%, 20% to 22%. Different coated pellets were prepared and the corresponding release profile was measured by a pharmatest tester. The delayed-release time of drug from coated pellets at 6%, 9%, 12%, 15%, 18%, 20% and 22% outer coating level was 0.5, 1.5, 2.0, 2.5, 4.0, 5.5 and 7 h, respectively. The results (Fig. 4) demonstrate that with the increase in thickness of the rupturable layer, the delayed-release time of coated pellets increased and the release rate after the lag time decreased. It indicated that the coating level of rupturable layer had significant effect on the lag time of coated pellets.

2.5. Effect of pH value of the dissolution medium on drug release

The release profile of drug from coated pellets at 18% coating load of both swelling layer (containing 1.5% SDS) and rupturable layer was investigated in distilled water, 0.1 mol/L HCl, pH 6.8 phosphate buffer solution (PBS) and the simulated GI pH conditions (0.1 mol/L HCl for 2 h, then adjusted to pH 6.8), respectively. The results (Fig. 5) indicate that the release behavior of drug from coated pellets had no significant difference in distilled water, pH 6.8 PBS and the simulated GI pH conditions, but in 0.1 mol/L HCl the lag time of drug release was obviously prolonged and the release rate remarkably decreased. The reason was probably that SDS, as an anionic surfactant, could play the role of the surface active action only in the ionic state. In acidic medium only 10% of SDS was ionized and its weak wetting action hampered the penetration of water into the swelling layer, and thus the swelling layer expanded so slowly that the lag time was obviously prolonged and the release rate remarkably decreased. On the contrary, in basic medium SDS was ionized completely and could play the wetting action adequately, which accelerated water penetration and made the swelling layer expand rapidly. Consequently the lag time of drug release was shortened and the release rate increased greatly.

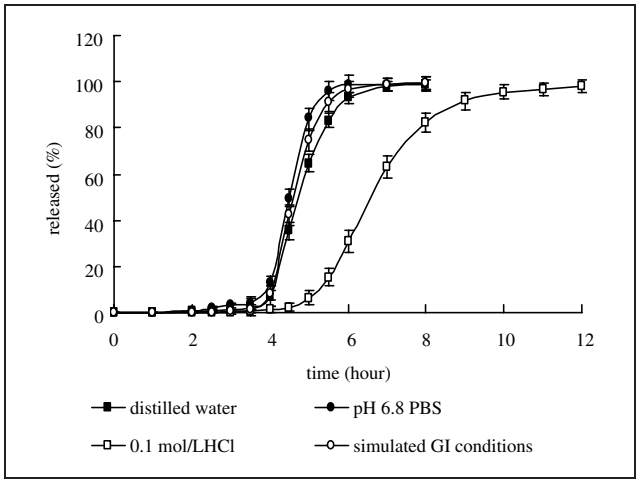

Fig. 5: Effect of the pH values of dissolution medium on the release profiles

2.6. Effect of rotating speed of dissolution tester on drug release

The release behavior of drug from the coated pellets at 18% coating load of both swelling layer (containing 1.5% SDS) and rupturable layer was measured in distilled water at rotating speeds of 100, 75 and 50 rpm. The results (Fig. 6) show that the delayed-release time of coated pellets decreased and the release rate after the lag time increased as the rotating speed increased.

2.7. Release profiles of hydroxysafflor yellow A, Panax notoginseng saponins and ferulic acid from Shuxiong sustained-release capsules (SXSRC) in vitro

SXSRC were prepared by encapsulating the different pellets at 0%, 9%, 15%, 18% and 20% coating level of the rupturable layer into hard gelatin capsules at equal ratio. The release profiles of hydroxysafflor yellow A, *Panax notoginseng* saponins and ferulic acid from SXSRC were tested under simulated gastrointestinal pH conditions. The value of similarity factor (f_2) of hydroxysafflor yellow A and *Panax notoginseng* saponins, hydroxysafflor yellow A and ferulic acid, *Panax notoginseng* saponins and ferulic acid was 90.1, 77.3, 87.0, respectively. The results (Fig. 7) demonstrate that the release behaviors of various compositions from SXSRC were not significantly different and exhibited obvious sustained-release characteristics under simulated gastrointestinal pH conditions.

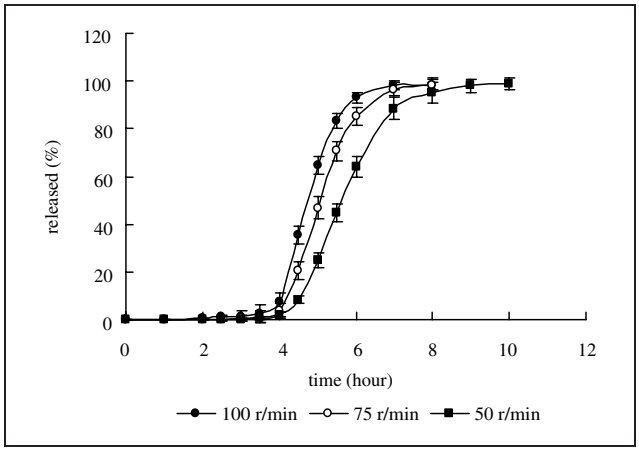

Fig. 6: Effect of the dissolution rotational speed on the release profiles

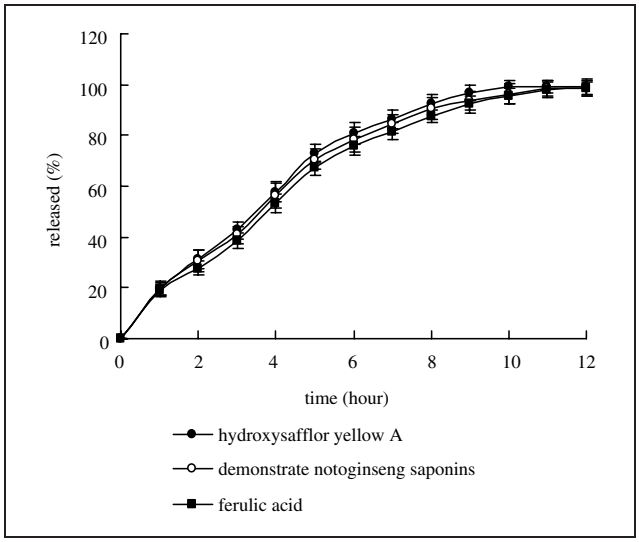

Fig. 7: Release profiles of hydroxysafflor yellow A, panax notoginseng saponins and ferulic acid from SXSRC

3. Discussion

In this study Shuxiong coated pellets were prepared by taking L-HPC as the swelling agent because its superior swelling behavior after absorbing water could cause higher internal swelling pressure than CMS-Na, PVPP, CC-Na and CMC-Ca. Furthermore, the coated pellets with L-HPC as the swelling agent exhibited time-controlled release characteristics as expected. The addition of SDS at an appropriate ratio into the swelling layer could accelerate the penetrating rate of water and thus the resultant internal pressure could reach and exceed the critical swelling pressure more rapidly. This caused the rupturing of the EC coating, at the same time the drug was released promptly. The increase in thickness of the swelling layer could force the outer coating to break more quickly after absorbing water, which obviously made the release rate of drug from the coated pellets increase. But when the thickness of the swelling layer was up to a certain extent, the increase in coating thickness had no significant effect on drug release.

The thickness of the rupturable layer had great influence on the break of the outer coating after the coated pellets absorbed water. With the increase in thickness of the rupturable layer the lag time of coated pellets distinctly increased and the release rate after the lag time remarkably decreased. The rotating speed of the dissolution tester had a certain effect on the release behavior of drug from the pellets. As the rotating speed increased the delayed-release time of coated pellets decreased and the release rate after the lag time increased. The pH value of the dissolution medium also influenced drug release because it could affect the ionization of SDS in the swelling layer. In acidic medium the lag time of the coated pellets was prolonged and the release rate decreased. On the contrary, in basic medium the lag time of the coated pellets decreased and the drug release was accelerated greatly. Since the residence time of SXSRC in stomach was only 2 h after the oral administration, it could be speculated that the pH value had no significant effect on the release behavior of drug from pellets *in vivo*, and that was preliminarily testi-

fied by the results of release rate test of drug from SXSRC in simulated gastrointestinal fluid.

After formulation and coating level of swelling layer were fixed, the coated pellets would release active compositions in different expected time through regulating the coating level of the rupturable layer. Several kinds of coated pellets whose rupturable layer had different coating levels were mixed and encapsulated into hard gelatin capsules to obtain SXSRC. In the dissolution medium, the various kinds of coated pellets in SXSRC could release active compositions successively in accordance with time and showed sustained-release characeristics as a whole. Because the outer EC film of different pellets in SXSRC could rupture successively after absorbing water, and then all components containing in coated pellets were released abruptly due to the strong rupturing of the coating, it would be possible that the various components in SXSRC with different physicochemical properties could release synchronously while sustained-releasing. That complies with the organic whole conception of compound compatibility of TCMCR and achieves the expected objective. To study the pharmacokinetics of SXSRC after oral administration further investigatious are needed.

4. Experimental

4.1. Materials

Ferulic acid, hydroxysafflor yellow A and *Panax notoginseng* saponins were provided by National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). The refined extracts from root of *Panax notoginseng*, flower of *Carthamus tinctorius* and rhizoma of *Ligusticum chuanxiong* were prepared in this laboratory. Model 60RT-5 HPMC (viscosity of 5 mPas) was from Feicheng Ruitai Fine Chemical Co. Ltd. (Shandong, China). L-HPC was supplied by Yingkou Aoda Medical excipient factory (Liaoning, China). CMS-Na and PVPP were obtained from BASF Corp., USA. CC-Na and CMC-Ca were supplied from Shin-Etsu Chemical Co. Ltd. (Tokyo, Japan). SDS was obtained from Haosen Pharmaceutical Co. Ltd. (Zhejiang, China). Microcrystalline (MCC) was from Changshu Medical excipient factory (Jiangsu, China). EC aqueous dispersion (Surelease®, 25%, w/w) was provided by Colorcon Coating Technique Co. Ltd. (Shanghai, China). Methanol used was of HPLC grade and all other reagents used were of analytical grade.

4.2. Instruments

Model BZJ-360M coating granulator (Beijing Tianmin High-tech Development Co., China); Mini-fluidized bed spray coater (Shenyang Pharmaceutical University, China); Model UV-2501PC UV-VIS spectrophotometer (Shimadzu, Japan); Model 510 HPLC system (Waters, USA); Kromasil C_{18} analytical column (Tianjin Tianhe Chromatographic Apparatus Ltd. Co., China); Model ZRD6-A intelligent pharmatest tester (Shanghai Huanghai Pharmatest Apparatus Factory, China).

4.3. Preparation of SXSRC

4.3.1. Preparation of core pellets loading drugs

First, the refined extracts from root of *Panax notoginseng*, flower of *Carthamus tinctorius* and rhizoma of *Ligusticum chuanxiong* were mixed adequately with MCC at a certain ratio. Then, Shuxiong pellets were prepared in a coating granulator using 3% HPMC (5 mPas) solution as adhesive agent. The technical parameters were as follows: rotor rotating rate, 200 rpm; blower rate, 10×20 L/min; the rate of air flow, 15 L/min; spray air pressure, 0.5 MPa; rotating rate of spray solution pump, 14 rpm; and rotating rate of power feed machine, 18 rpm. Finally, drug-loaded pellets were dried in an oven at 50 °C for 2 h and the dried pellets (20–30 mesh) were screened for the coating procedure.

4.3.2. Preparation of coating solution

A solution of HPMC (0.5%, w/w) was prepared by dissolving HPMC powder in the water. L-HPC (3%, w/w) and SDS (1.5%, w/w) were then added to the HPMC solution by stirring until a homogeneous solution was obtained. The uniform solution was used as the coating solution of swelling layer. Surelease® was diluted with water to obtain 8% (w/w) EC aqueous dispersion as the coating solution of rupturable layer.

4.3.3. Coating of Shuxiong pellets and preparation of SXSRC

The core pellets (20–30 mesh) were coated in the mini-fluidized bed spray coater with the base-spray method. The coating solution of swelling layer was used as inner coating solution and EC aqueous dispersion as outer coating solution, respectively. The process conditions were as follows: outlet air temperature, 37 °C ± 2 °C; speed of spraying inner coating solution, 1.5 mL/min; speed of spraying outer coating solution, 0.5 mL/min; modulation frequency of blower, 25 Hz; atomized air pressure, 0.25 MPa. The coating solution was stirred continuously during spraying. The coated pellets were further dried in the bed for 10 min after the coating process was finished and then placed in the oven at 40 °C for 2 h to remove the residual solvent. Keeping the coating load of the inner layer as 18%, four kinds of coated pellets were prepared with an outer coating level of 9%, 15%, 18% and 20%, respectively. Finally, the core pellets and these four kinds of coated pellets with different release patterns were encapsulated into hard gelatin capsules at certain ratio to obtain SXSRC.

4.4. Determination

4.4.1. Determination of hydroxysafflor yellow A

Shuxiong coated pellets were ground into fine powder. An aliquot (100 mg) of the powder was dispersed in 100 ml water and ultrosonicated for 30 min. Being filtered, the filtrate was diluted with water as sample solution. Absorption of solution was detected by UV at 401 nm for assay of hydroxysafflor yellow A content.

4.4.2. Determination of Panax notoginseng saponins

An aliquot (500 mg) of the fine powder of pellets was dispersed in 100 ml methanol and ultrosonicated for 30 min. Being filtered, the filtrate was evaporated to dryness. The residue was dissolved in 10 ml of water and the solution was transferred into D_{101} macroporous polymeric adsorbent column. After the column was washed with water till no polysaccharide reaction occurred, the sample was eluted with 70% ethanol, and the eluate was collected and evaporated to dryness. The residue was dissolved in methanol and transferred to a 25 ml measuring flask, and then diluted to the mark with methanol. The solution was briefly shaken and used as sample solution. A sample solution of 40 µl was transferred to a glass tube with stopper and evaporated to dryness at low temperature. After 0.2 ml of 5% vanillin glacial acetic acid and 0.8 ml of perchloric acid were added into the tube, the tube was placed in the water bath at 60 °C for 15 min and then was taken out and placed in the ice bath to cool for 2–3 min. The glacial acetic acid of 5.0 ml was added into the tube with brief shaking. The solution with the suite reagent was used as the blank solution. Absorption of solution was detected by UV at 560 nm for assay of *Panax notoginseng* saponins content.

4.4.3. Determination of ferulic acid

Determination of ferulic acid in pellets was performed by a HPLC system. Chromatographic separation was carried out on a Kromasil C_{18} analytical column (200 mm × 4.6 mm, 10 µm) with a column temperature of 25 °C. The mobile phase consisted of methanol and glacial acetic acid in the ratio of 40 : 60 (v/v) (adjusted to pH 4.9 with triethylamine) at a 1.0 ml/min flow rate. The UV detector wavelength was set at 280 nm. An aliquot (500 mg) of the fine powder of pellets was dispersed in 100 ml methanol and ultrosonicated for 30 min. Being filtered, 10 µl of the filtrate were injected in the HPLC system. Peak area was detected for assay of ferulic acid content.

4.5. Dissolution test

4.5.1. Dissolution test of hydroxysafflor yellow A

According to the first method of the second section of Chinese pharmacopoeia 2005, the release behavior of hydroxysafflor yellow A from the coated pellets was measured by an intelligent pharmatest tester at a rotating speed of 100 rpm and at 37 °C ± 0.5 °C in 900 ml of dissolution medium. A series of 5.0 ml of samples were removed at predetermined time points and filtered through microporous filtering film (0.8 µm), and then 5.0 ml of medium maintained at 37 °C ± 0.5 °C was added. Absorption of sample solution was detected by UV as described previously. With the content of hydroxysafflor yellow A in pellets being 100%, the cumulative release percentage of hydroxysafflor yellow A was calculated.

4.5.2. Dissolution test of Panax notoginseng saponins

The release behavior of *Panax notoginseng* saponins from the coated pellets was measured by the same testing apparatus and method as hydroxysafflor yellow A. The 5 ml of sample solution was analyzed by UV as described previously. With the content of *Panax notoginseng* saponins in pellets being 100%, the cumulative release percentage of *Panax notoginseng* saponins was calculated.

4.5.3. Dissolution test of ferulic acid

The release behavior of ferulic acid from the coated pellets was measured by the same testing apparatus and method as hydroxysafflor yellow A. Sample solution was collected and determined by HPLC as described previously. With the content of ferulic acid in pellets being 100%, the cumulative release percentage of ferulic acid was calculated.

References

Bussemer T, Peppas NA, Bodmeier R (2003) Evaluation of the swelling, hydration and rupturing properties of the swelling layer of a rupturable pulsatile drug delivery system. Eur J Pharm Biopharm 56: 261–270.

Chinese Pharmacopoeia Commission (2005) Shuxiong Pian, in the First Section of Pharmacopoeia of the People's Republic of China 2005 Edition, Chemical Industry Press, Beijing, pp. 636.

Krögel I, Bodmeier R (1999) Floating or pulsatile drug delivery systems based on coated effervescent cores. Int J Pharm 187: 175–184.

Li XD, Pan WS, Nie SF, Wu LJ (2004) Studies on controlled release effervescent osmotic pump tablets from Traditional Chinese Medicine Compound Recipe. J Control Release 96: 359–367.

Liu X, Lin Y, Yu LR (2001) Study on Xiaojin Cinnabar floated sustained release preparation. Chin Tradit Pat Med 23 (2): 87–89.

Morita R, Honda R, Takahashi Y (2000) Development of oral controlled release preparations, a PVA swelling controlled release system (SCRS). I. Design of SCRS and its release controlling factor. J Control Release 63: 297–304.

Qiu MF, Mo SW, Luo HY, Yang YY, Liu N, Jia W, Peng T (2005) Calcium antagonizing effect of compound Danshen sustained-release tablet and comprehensive evaluation of sustained-release effect *in vitro*. Chin Tradit Herb Drugs 36 (3): 354–358.

Song HT, Guo T, Zhang RH, Zheng CL, Ma Y, Li X, Bi KS, Tang X (2002) Preparation of the traditional Chinese Medicine Compound recipe heart-protecting musk pH-dependent gradient-release pellets. Drug Dev Ind Pharm 28: 1261–1273.

Song HT, Guo T, Zhang YX, Zhong J, Zhou JP, Zhou J (2003) Preparation of salbutamol sulfate pulsatile controlled-release pellets. J Shenyang Pharm Univ 20 (2): 97–100.

Song HT, Guo T, Kang LP, Jiang P, Chen DW, He ZG (2005) Studies on Shuxiong sustained-release capsules prepared by using multiparticulate site-controlled release technology. Chin Tradit Herb Drugs 36 (7): 993–998.

Sungthongjeen S, Puttipipatkhachorn S, Paeratakul O, Dashevsky A, Bodmeier R (2004) Development of pulsatile release tablets with swelling and rupturable layers. J Control Release 95: 147–159.

Ueda S, Hata T, Asakura S, Yamaguchi H, Kotani M, Ueda Y (1994a) Development of a novel drug release system, time-controlled explosion system (TES). I. Concept and design. J Drug Target 2: 35–44.

Ueda S, Yamaguchi H, Kotani M, Kimura S, Tokunaga Y, Kagayama A, Hata T (1994b) Development of a novel drug release system, time-controlled explosion system (TES). II. Design of multiparticulate TES and *in vitro* drug release properties. Chem Pharm Bull 42: 359–363.

Ueda S, Ibuki R, Kimura S, Murata S, Takahashi T, Tokunaga Y, Hata T (1994c) Development of a novel drug release system, time-controlled explosion system (TES). III. Relation between lag time and membrane thickness. Chem Pharm Bull 42: 364–367.

Wei SH, He ZG, Wang LY (2003) Preparation of sinomenine hydrochloride oral osmotic pump-controlled release tablets and the factor influencing the drug release rate. J Shenyang Pharm Univ 20 (3): 165–169.