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RESEARCH PAPER

Preparation of the Traditional Chinese Medicine Compound Recipe Heart-Protecting Musk pH-Dependent Gradient-Release Pellets

Hongtao Song,[1,*] Tao Guo,[1] Ruhua Zhang,[2] Chunli Zheng,[2] Yan Ma,[2] Xian Li,[2] Kaishun Bi,[2] and Xing Tang[2]

[1]*Department of Pharmacy, The General Hospital of Shenyang Military Region, Shenyang 110016, China*
[2]*Shenyang Pharmaceutical University, Shenyang 110016, China*

ABSTRACT

In this study a sustained-release formulation of traditional Chinese medicine compound recipe (TCMCR) was developed by selecting heart-protecting musk pills (HPMP) as the model drug. Heart-protecting musk pellets were prepared with the refined medicinal materials contained in the recipe of HPMP. Two kinds of coated pellets were prepared by using pH-dependent methacrylic acid as film-forming material, which could dissolve under different pH values in accordance with the physiological range of human gastrointestinal tract (GIT). The pellets coated with Eudragit L30D-55, which dissolves at pH value over 5.5, were designed to disintegrate and release drug in the duodenum. The pellets coated with Eudragit L100–Eudragit S100 combinations in the ratio of 1:5, which dissolve at pH value 6.8 or above, were designed to disintegrate and release drug in the jejunum to ileum. The pellets coated with HPMC, which dissolves in water at any pH value, were designed to disintegrate and release drug in the stomach. Finally, the heart-protecting musk sustained-release capsules (HPMSRC) with a pH-dependent gradient-release pattern were prepared by encapsulating the above three kinds of coated pellets at a certain ratio in hard gelatin capsule. The results of dissolution of borneol (one of the active compounds of the TCMCR) in vitro demonstrated that

*Corresponding author. Fax: +86-24-23891093; E-mail: sohoto@sohu.com

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the coating load and the pH value of the dissolution medium had little effect on the release rate of borneol from pellets coated with hydroxypropyl methyl cellulose (HPMC), but had a significant effect on the release rate of borneol from pellets coated with Eudragit L30D-55 or Eudragit L100–Eudragit S100 combinations in the ratio of 1:5. The pellets coated with Eudragit L30D-55 at 30% (w/w) coating load or above had little drug release in 0.1 mol/L HCl for 3 hr and started to release drug at pH value over 5.5. The pellets coated with Eudragit L100–Eudragit S100 combinations in the ratio of 1:5 at 36% (w/w) coating load or higher had little drug release in 0.1 mol/L HCl for 3 hr and in phosphate buffer of pH value 6.6 for 2 hr, and started to release drug at pH value 6.8 or above. The release profiles of lipophilic bornoel and hydrophilic total ginsenoside from HPMSRC, consisting of three kinds of pellets respectively coated at a certain ratio with HPMC, Eudragit L30D-55, and Eudragit L100–Eudragit S100 in the ratio of 1:5, showed a characteristic of pH-dependent gradient release under the simulated gastrointestinal pH conditions and no significant difference between them. The results indicated that various components with extremely different physicochemical properties in the pH-dependent gradient-release delivery system of TCMCR could release synchronously while sustained-releasing. This complies with the organic whole concept of compound compatibility of TCMCR.

Key Words: *Borneol; Heart-protecting musk pellets; pH-Dependent gradient-release delivery system; Sustained-release formulations; Total ginsenoside; Traditional Chinese medicine compound recipe*

INTRODUCTION

Traditional Chinese medicine compound recipe (TCMCR) is a precious heritage of Chinese medicine and has made a prominent contribution to the prosperity of the Chinese nation and the formation and development of world medicine. In recent years, quite considerable progress has been made in the dosage forms of TCMCR. The novel dosage forms such as dripping pill, microcapsule, aerosol, granule without sugar, power injection, and soft capsule were prepared and studies on mucosa and transdermal drug delivery of TCMCR were reported.[1] However, formulations of TCMCR have a large gap in quality compared with those of chemical medicine, and need to be improved. Up to now, no studies on sustained- or controlled-release formulations of TCMCR were reported. In fact, the characteristic of traditional Chinese medicine in treating illness lies in the application of TCMCR, single herb or animal medicine is rarely used. In this paper, a sustained-release formulation of TCMCR was developed by selecting heart-protecting musk pills (HPMP) as the model drug.

Listed in the first section of the Pharmacopoeia of the People's Republic of China 2000 Edition (ChP 2000), HPMP consist of *Moschus*, the extract of *Radix Ginseng*, *Venenum Bofonis*, *Borneolum*, *Styrax*, *Cortex Cinnamomi*, and *Artificial Calculus Boris*. They produce reliable clinical effects on eliminating cold-phlegm for resuscitation by means of aromatics and supplementing *qi* to strengthen the heart. They are primarily applied to the treatment of chest distress, angina pectoris, and myocardial infarction caused by coronary heart disease.[2,3] In order to prepare the sustained-release formulations, some medicinal material in the original prescription was refined in the previous studies.[4–7] The total ginsenoside was extracted from *Radix Ginseng* with 40% alcohol and purified with D_{101} macroporous polymeric adsorbent. Water steam distillation was applied to extract the cinnamic oil from *Cortex Cinnamomi*. The spray-drying technique was used to dry total ginsenoside and water extract of *Cortex Cinnamomi* in liquid state. The beta-cyclodextrin (β-CD) inclusion complexes of borneol, cinnamic oil, storax, and artificial musk were formulated and identified by the methods of thin-layer chromatography (TC), differential scanning calorimetery (DSC), differential thermal analysis (DTA), infrared spectroscopy (IR), and x-ray diffraction.

The techniques of preparation of β-CD inclusion complexes were optimized by using a uniform design. Compared with the mixture, the solubility and dissolution rate of inclusion complexes were increased in various media, and the stability of inclusion complexes toward light, heat, and humidity was also improved remarkably.[8–11] Based on the above work, the heart-protecting musk pellets were prepared in a centrifugal granulator by using microcrystalline (MCC) as fillers and 2% hydroxypropyl methyl cellulose (HPMC) solution as adhesive agent.

Ingredients in HPMP, made up of seven kinds of traditional Chinese medicinal materials, were considerably numerous and had extremely different physicochemical properties, including hydrophilic ginsenoside and lipophilic borneol, muscone, cinnamic aldehyde, etc. The mechanisms of these ingredients to treat angina pectoris and myocardial infarction caused by coronary heart disease were different from each other and had their own characteristics. Only when they were released and absorbed synchronously in vivo could they cooperate with and supplement each other, which complies with the organic whole concept of compound compatibility of traditional Chinese medicine. Separation of any segment would deviate from the fundamental theory of traditional Chinese medicine, and affect therapeutic efficacy.

The variation of the pH values in the healthy human gastrointestinal tract (GIT) has already been measured by pH-sensitive radiotelemetry technology. The pH values in the stomach were in the range 1.2 to 5.0, the pH values in the duodenum, jejunum, ileum, and colon were 6.63 ± 0.53, 7.41 ± 0.36, 7.49 ± 0.46, and 6.63 ± 0.67, respectively.[12,13] Moreover, it was reported in many articles that the average gastric emptying time of pellets was in the range 1–3 hr in a fasted state and 2–4 hr in a fed state. The average transit time of pellets in the small intestine was 3 hr or so, whether food was present or absent. It takes 5–7 hr for pellets to arrive at the colon after oral administration. When the density of pellets was less than 2.4 g/cm^3, there was no difference in gastrointestinal transit time of pellets at different densities. Once densities were above 2.8 g/cm^3, the gastric emptying time of pellets increased markedly (>1 hr), but the intestinal transit time was not affected by the variations in density. In addition, pellets have better reproducibility and uniformity in comparison with tablets in terms of the transit time in the gastrointestinal tract.[14–20]

Therefore, according to the physiological pH values of human GIT, two kinds of coated pellets were prepared with pH-dependent methacrylic acid as film-forming material, which could dissolve at different pH values.[21–23] The pellets coated with Eudragit L30D-55, which dissolves at pH value over 5.5, were expected to disintegrate and release drug in the duodenum. The pellets coated with Eudragit L100–Eudragit S100 combination 1:5, which dissolves at pH value 6.8 or above, were expected to disintegrate and release drug in the jejunum to ileum. The pellets coated with HPMC, which is a water-soluble polymer, were expected to disintegrate and release drug in the stomach. The above three kinds of pellets were filled into a hard gelatin capsule at a certain ratio to obtain heart-protecting musk sustained-release capsules (HPMSRC) with a pH-dependent gradient-release pattern.

MATERIALS AND METHODS

Materials

Hydroxypropyl methyl cellulose (HPMC) (Methocel E5, manufactured by Dow Chemical Co., Michigan, USA) was supplied by Colorcon (Shanghai, China). Methacrylic acid copolymers (Eudragit L30D-55, Eudragit L100, Eudragit S100) were supplied by Röhm GmbH Chemische Fabrik, Darmstadt, Germany. The plasticizer, triethyl citrate (TEC), used for coating was also obtained from Lancaster Company, Lancashire, U.K. Other excipients used to prepare the pellets were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

Preparation of Heart-Protecting Musk Pellets

The amount of ingredients used in the formulation of heart-protecting musk pellets was as follows: 1.0% (w/w) total ginsenoside, 4.5% (w/w) β-CD inclusion complexes of artificial musk, 25.0% (w/w) β-CD inclusion complexes of borneol, 1.0% (w/w) β-CD inclusion complexes of cinnamic oil, 12.0% (w/w) β-CD inclusion complexes of storax, 10.0% (w/w) β-CD inclusion complexes of toad venom, 2.0% (w/w) extract of *Cortex Cinnamomi*, 1.5% (w/w) *Artificial Calculus Boris*, 43.0% (w/w) MCC. The heart-protecting musk pellets were prepared in a centrifugal granulator (Model BZJ-360M, Beijing Tianmin High Technology Development Co., China)

by using MCC as filler and 2% HPMC solution as adhesive agent. The process parameters were as follows: rotor rotating rate, 200 rpm; blower rate, 10×20 L/min; 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 12 hr.

Preparation of HPMC Coating Solution

A solution of HPMC in water was prepared by dispersing 80 g of HPMC powder in 300 mL of preheated water (80–90°C), stirring for 2 hr, diluting with an additional 700 mL of cold water, and allowing it to stand until uniform and cool.

Preparation of Eudragit L30D-55 Aqueous Dispersion for Coating

The formulation of Eudragit L30D-55 aqueous dispersion was as follows: 26.5% (w/w) Eudragit L30D-55, 0.8% (w/w) TEC, 4.0% (w/w) micronized talc, 68.7% (w/w) distilled water. The suspension was prepared by dispersing TEC and micronizing talc in water while being homogenized in a high-speed disperse mill (Model BM8-100L, Shanghai Weiyu Machinery and Electrical Manufacturing Co. Ltd., China). The suspension was slowly added to the Eudragit L30D-55 dispersion while being stirred and then the dispersion was passed through a sieve of mesh 0.2 mm. The final coating dispersion contains 8% polymer.

Preparation of Coating Solution of Eudragit L100–Eudragit S100 Aqueous Dispersion

The formulation of Eudragit S100 aqueous dispersion was as follows: 8% (w/w) Eudragit S100, 4% (w/w) TEC, 4.06% (w/w) 1 mol/L NH_3, 2.64% (w/w) micronized talc, 81.3% (w/w) distilled water. The formulation of Eudragit L100 aqueous dispersion was as follows: 8% (w/w) Eudragit L100, 4% (w/w) TEC, 2.71% (w/w) 1 mol/L NH_3, 4% (w/w) micronized talc, 81.3% (w/w) distilled water. According to the above-mentioned formulations respectively, Eudragit S100 or Eudragit L100 was added into water separately while being stirred, making sure that the powder was quickly wetted and no lump formed. After stirring for about 5 min, the ammonia solution was added with stirring by means of a peristaltic pump and stirring continued for another 60 min. The TEC was then added to the dispersion while stirring for a further 60 min. Micronized talc was suspended in surplus water while homogenizing in a high-speed disperse mill. The talc suspension was added to the above aqueous dispersion, and then the dispersion was passed through a sieve of mesh 0.2 mm. After the aqueous dispersions were prepared separately, Eudragit L100 and Eudragit S100 aqueous dispersions were mixed in a ratio of 1:5. The mixing order was that the Eudragit S100 dispersion was slowly added to the Eudragit L100 dispersion while stirring carefully. The final coating dispersion contains 8% polymer.

Coating of Heart-Protecting Musk Pellets

Heart-protecting musk pellets were coated in a mini fluid-bed spray coater (Shenyang Pharmaceutical University, China) by spraying the coating dispersion continuously from the bottom of the bed. The operating conditions were as follows: atomized air pressure, 0.2 MPa; rate of peristaltic pump, 60 rpm; outlet air temperature, 33 ± 1°C. The coating dispersion was stirred continuously during spraying. After coating, the pellets were dried in the bed at the same temperature for about 5 min and then put in an oven at 40°C for 2 hr. Three kinds of pellets were prepared by coating with three types of polymers or a mixture of polymers, i.e., coating with HPMC, Eudragit L30D-55, and Eudragit L100–Eudragit S100 combinations 1:5, respectively. The loads of coatings were as follows: 2% and 4% (w/w, total solid applied) for HPMC; 20%, 30%, and 40% (w/w, total solid applied) for Eudragit L30D-55; 24%, 36%, and 48% (w/w, total solid applied) for Eudragit L100–Eudragit S100 combinations 1:5.

Calculation of the Thickness of the Coating Layer

In order to resist the effect of gastric acid, the coating layer of methacrylic acid copolymers has to come up to a certain thickness. The thickness of the coating layer was estimated roughly by the percentage of coating load, because of its troublesome measurement. Certainly, the amount of coating material is related to the surface area of the pellets, so the thickness of the coating layer should be expressed in weight (mg) of dry polymer substance per square centimeter of surface area (L, mg/cm^2).

The relation between L and the percentage of coating load (M) can be calculated according to the following equation:

$$L = \frac{MNW \times 100}{S \times 10{,}000}$$

where L is the weight (mg) of dry polymer substance per square centimeter of surface area, M is the percentage of coating load (%, w/w), N is the percentage of polymer weight in total solid weight of coating solution (%, w/w), W is the weight (mg) per pellet, and S is the surface area (cm^2) per pellet.

Determination of Borneol Content in the Coated Pellets

Determination of borneol content in the coated pellets was performed in the GC system (Model GC-8A, Shimadzu, Japan). A spiral glass column (Φ 2.6 mm×3.0 m) was packed with chromosorb W (AW) (60–80 mesh) with 10% PEG-20M as stationary liquid. The isothermal temperature was 145°C for the column and 210°C for the injector and hydrogen flame ionization detector. The pressures were 9.8×10^4 Pa for carrier gas (nitrogen), 6.86×10^4 Pa for hydrogen and 4.9×10^4 Pa for air, respectively. Naphthalene was used as the internal standard.

Heart-protecting musk coated pellets were ground into fine powder. An aliquot (200 mg) of the powder was transferred into a 15 mL centrifuge tube with a stopper, and 10 mL of ethanol was added. The mixture was ultrasonicated for 30 min and allowed to stand overnight. The next day, the mixture was centrifuged at 2500 rpm for 10 min. The supernatant liquid was passed through a 0.45-μm membrane filter. The filtrate was used as sample solution. The 4.0 mL of sample solution and 0.2 mL of internal standard ethanol solution (2.0 mg naphthalene per milliliter) were transferred into a 5 mL measuring flask and diluted to mark with ethanol. The solution was briefly shaken and 1.0 μL of the solution was injected into the chromatographic system for assay of borneol content.

Determination of Total Ginsenoside Content in the Coated Pellets

An aliquot (5.0 g) of the powder of heart-protecting musk coated pellets was dispersed in 100 mL ethanol and ultrasonicated for 30 min. Being filtered, the filtrate was evaporated to approximately 5 mL and mixed with 2.0 g of diatomaceous earth, and then evaporated to dryness. The mixture was placed into the sorbitic extractor and heated in the bath to degrease with chloroform for 2 hr. The degreased power was extracted continuously in the sorbitic extractor with methanol for 5 hr. Methanol of the extracted solution was retrieved and the residue dissolved with 10 mL of water. Then the solution was transferred into a D_{101} macroporous polymeric adsorbent column. Afterwards, 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 5 mL of methanol and transferred to a 10-mL measuring flask, then diluted to mark with methanol.

A sample solution of 40 μL was transferred to a glass tube with a 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 to the tube, the tube was placed in the water bath at 60°C for 15 min and then taken out and placed in the ice bath to cool for 3 min. Glacial acetic acid, 5.0 mL, was added to the tube with brief shaking. The solution with the suite reagent was used as the blank solution. Absorption of solution was detected by UV (Model UV-160A, Shimadzu, Japan) at 560 nm.

Dissolution Test of Borneol

According to the third method of the second section of ChP 2000, the dissolution behavior of borneol from the pellets was measured by a pharmatest tester (Model ZRD6-A, Shanghai Huanghai Pharmatest Apparatus Factory, China) at a rotating speed of 100 rpm and at 37 ± 0.5°C in 300 mL of dissolution medium with an airtight vessel. A series of 1.0 mL samples were removed at predetermined time points and filtered through microporous filtering film (0.8 μm) and then 1.0 mL of medium maintained at 37 ± 0.5°C was added. The 0.3 mL of naphthalene ethyl acetate solution (0.02 mg/mL) and 0.7 mL of sample were vortex-mixed for 5 min and centrifuged at 5000 rpm for 10 min. The upper organic phase of 1.0 μL was injected into the GC system for assay of borneol content. With the content of borneol of coated pellets being 100%, the cumulative release percentage of borneol was calculated.

To study the effect of the coating load on the release of borneol, the dissolution behaviors of borneol from pellets coated with HPMC at three levels (0%, 2%, and 4% load, w/w) were measured in 0.1 mol/L HCl for 2 hr. The dissolution behaviors of borneol from pellets coated with Eudragit L30D-55 at three levels (20%, 30%, and 40% load, w/w) were measured in 0.1 mol/L HCl for 2 hr and then in pH 6.6 phosphate buffer for 2 hr. The dissolution behaviors of borneol from pellets coated with Eudragit L100–Eudragit S100 1:5 at three levels (24%, 36%, and 48% load, w/w) were tested in 0.1 mol/L HCl for 2 hr, then in pH 6.6 phosphate buffer for 2 hr, and finally in pH 7.5 phosphate buffer for 3 hr.

To study the effect of the pH of the dissolution media on the release of borneol, the dissolution behaviors of borneol from pellets coated with HPMC at 2% coating load were measured in 0.1 mol/L HCl, in pH 2.5 and 5.0 phosphate buffer for 2 hr, respectively. The dissolution behaviors of borneol from pellets coated with Eudragit L30D-55 at 30% coating load were tested in pH 5.0, 6.1, 6.6, and 7.2 phosphate buffer for 2 hr, respectively. The dissolution behaviors of borneol from pellets coated with Eudragit L100–Eudragit S100 1:5 at 36% coating load were tested in pH 6.6, 6.8, 7.0, 7.2, 7.5, and 7.8 phosphate buffer for 2 hr, respectively.

Dissolution Test of Total Ginsenoside

According to the third method of the second section of ChP 2000, the dissolution behavior of borneol from the pellets was measured by a pharmatest tester at a rotating speed of 100 rpm and at $37 \pm 0.5^{\circ}C$ in 300 mL of dissolution medium. A series of 2.0-mL samples were removed at predetermined time points and filtered through microporous filtering film (0.8 μm) and then 2.0 mL of medium maintained at $37 \pm 0.5^{\circ}C$ was added. After three times extraction of the sample with 10 mL of chloroform, the chloroform solution was discarded. The aqueous solution was passed through a D_{101} macroporous polymeric adsorbent column. After washing with water, the column was eluted with 70% ethanol and the eluate collected and evaporated to dryness. The residues were determined according to the assay of total ginsenoside by UV. With the content of total ginsenoside of coated pellets being 100%, the cumulative release percentage of borneol was calculated.

Dissolution Test of Borneol and Total Ginsenoside from HPMSRC in the Simulated Gastrointestinal pH Conditions

The HPMSRC were prepared by encapsulating the pellets coated with HPMC at 2% coating load, Eudragit L30D-55 at 30% coating load, and Eudragit L100–Eudragit S100 1:5 at 36% coating load into hard gelatin capsules at a ratio of 1:1:1 (w/w/w). Then the release profiles of borneol and total ginsenoside from HPMSRC in the simulated gastrointestinal pH conditions were investigated. The dissolution behavior of borneol from HPMSRC was tested at pH 1.2 for 2 hr, pH 6.6 for 2 hr, and then pH 7.5 for 3 hr successively, corresponding to the pH values in the stomach, duodenum, and small intestine, respectively. The dissolution behavior of total ginsenoside from HPMSRC was tested at pH 5.0 for 2 hr, pH 6.6 for 2 hr, and then pH 7.5 for 3 hr successively, also corresponding to the pH values in the stomach, duodenum, and small intestine, respectively.

RESULTS

In this paper, the average weight per pellet calculated by weighing pellets and counting is 0.66 mg. According to the 1.0-mm average diameter of pellets, the surface area per pellet is 3.14 mm^2. The percentage of polymer weight was 62.35% of the total solid weight of Eudragit L30D-55 coating dispersion. When the coating loads were 20%, 30%, and 40%, the corresponding weight of dry polymer substance per square centimeter of surface area was 2.62 mg/cm^2, 3.93 mg/cm^2, and 5.24 mg/cm^2, respectively. The percentage of polymer weight was 54.64% of the total solid weight of Eudragit L100–Eudragit S100 of 1:5 coating dispersion. When the coating loads were 24%, 36%, and 48%, the corresponding weight of dry polymer substance per square centimeter of surface area was 2.76 mg/cm^2, 4.14 mg/cm^2, and 5.52 mg/cm^2, respectively.

The data presented in Fig. 1 demonstrate that the rate of release of borneol from the HPMC coated pellets is not affected by the amount of polymer applied (i.e., the coating load) within the range tested. And also, the pH of the dissolution media did not have any influence on the rate of release of the drug (borneol) from these pellets (Fig. 2).

The influences of the coating load of Eudragit L30D-55 and Eudragit L100–Eudragit S100 1:5 on

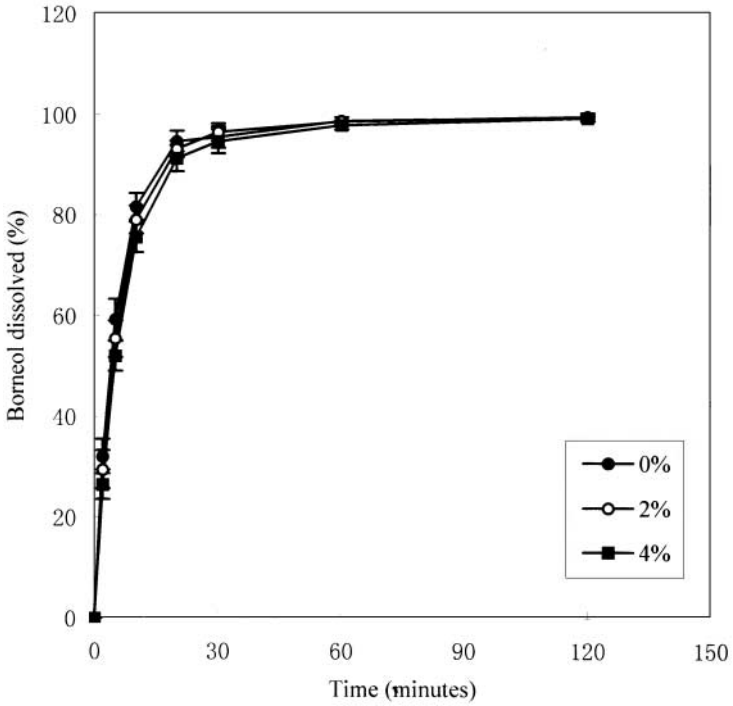

Figure 1. Effect of the coating load of HPMC on the dissolution rate of borneol from coated pellets with HPMC.

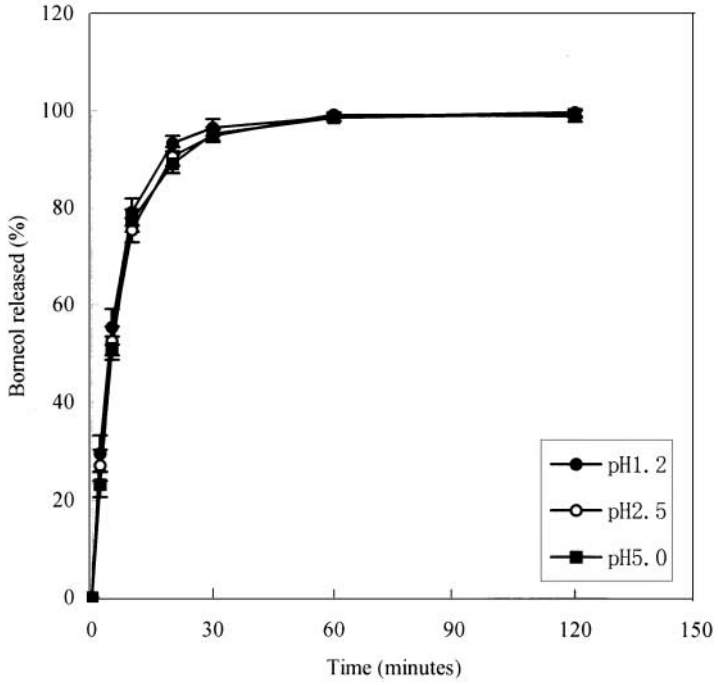

Figure 2. Effect of pH values of dissolution medium on the release of borneol from pellets coated with HPMC at 2% (w/w) coating load.

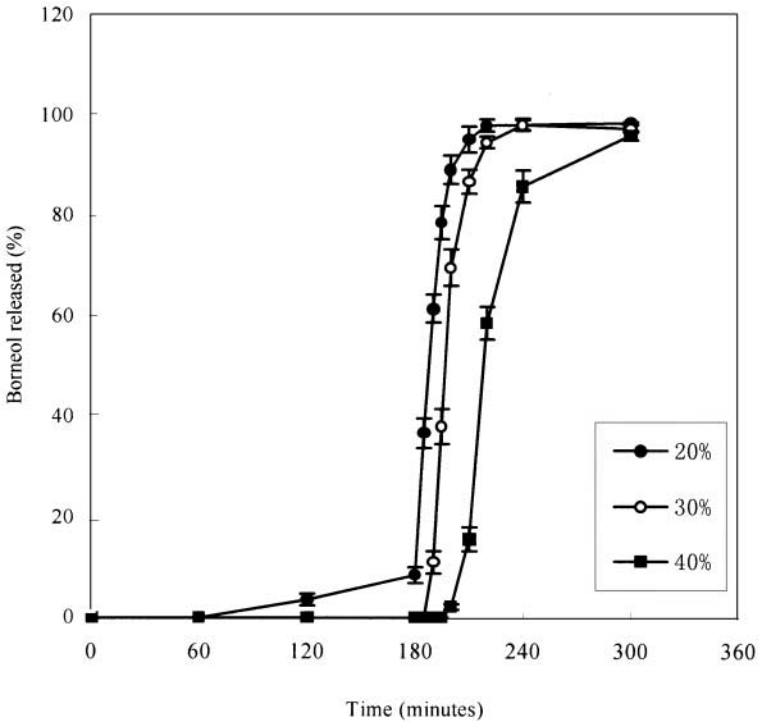

Figure 3. Effect of the coating load of Eudragit L30D-55 on the release rate of borneol from coated pellets with Eudragit L30D-55 in 0.1 mol/L HCl for 3 hr and pH 6.6 phosphate buffer for 3 hr.

the release rate of borneol from coated pellets are shown in Figs. 3 and 4, respectively. The accumulated released percentage of borneol from pellets coated with Eudragit L30D-55 at 20% coating load in 0.1 mol/L HCl for 3 hr was over 5%. The pellets coated with Eudragit L30D-55 at 30% and 40% coating load in 0.1 mol/L HCl for 3 hr had no drug release. The accumulated released percentage of borneol from pellets coated with Eudragit L100–Eudragit S100 1:5 at 24% coating load in 0.1 mol/L HCl for 3 hr and in pH 6.6 phosphate buffer for 2 hr exceeded 5%. The pellets coated with Eudragit L100–Eudragit S100 1:5 at 36% and 48% coating load in 0.1 mol/L HCl for 3 hr and in pH 6.6 phosphate buffer for 2 hr had no drug release.

The effects of the pH of the dissolution medium on the release rate of borneol from coated pellets are presented in Figs. 5 and 6, respectively. The data demonstrate that the pH of the dissolution medium had significant effects on the release of borneol from pellets coated with Eudragit L30D-55 at 30% coating load, which had no drug release at pH 5.0 for 2 hr. The release rate of borneol was slower at pH 6.1 than that at pH 6.6 and 7.2. The release of borneol showed no significant difference between pH 6.6 and 7.2. And also, the pH of the dissolution medium had a significant influence on the release of borneol from pellets coated with Eudragit L100–Eudragit S100 1:5 at 36% coating load, which had no drug release at pH 6.6 for 3 hr. The accumulated released percentage of borneol from the pellets in pH 6.8 for 3 hr was only about 40%. However, in the other three media, the drug release rate increased as the pH value increased.

There are many methods to compare the difference of drug release between a test preparation and a reference preparation or between two release profiles, for example, the time taken for x% of the drug to be released ($t_{x\%}$), the mean dissolution time ($MDT_{x\%}$), the similarity factor (f_2), or difference factor (f_1), and model dependence.[24–26] In this paper, the similarity factor was evaluated to compare the release profiles of borneol and total ginsenoside. Figure 7 shows that the release profiles of total ginsenoside and borneol from HPMSRC in the simulated gastrointestinal pH value conditions were similar ($f_2 = 79.6$).

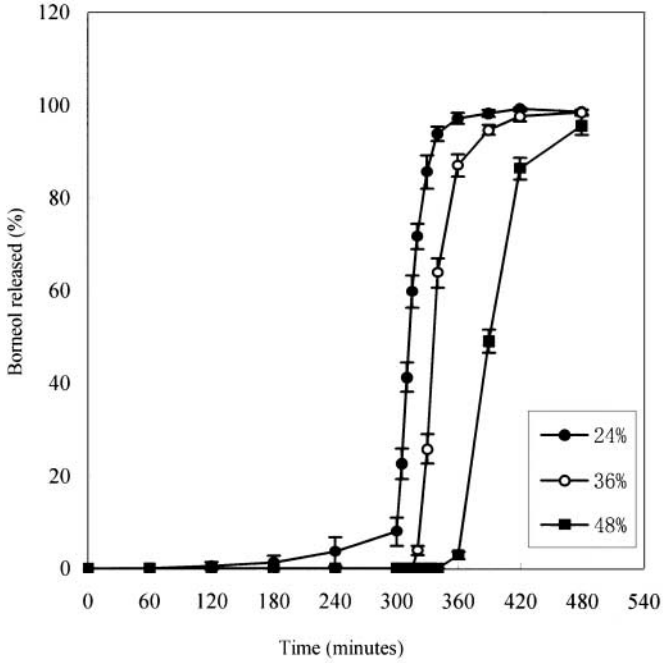

Figure 4. Effect of the coating load of Eudragit S100 L100–Eudragit S100 1:5 on the release rate of borneol from coated pellets with Eudragit L100–Eudragit S100 1:5 in 0.1 mol/L HCl for 3 hr, pH 6.6 phosphate buffer for 2 hr, pH 7.5 phosphate buffer for 2 hr.

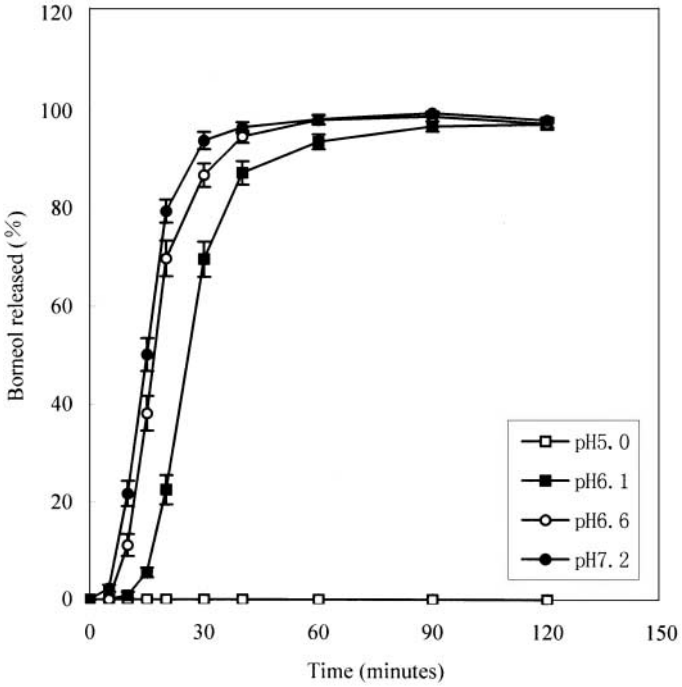

Figure 5. Effect of pH values of dissolution medium on the release of borneol from pellets coated with Eudragit L30D-55 at 30% (w/w) coating load.

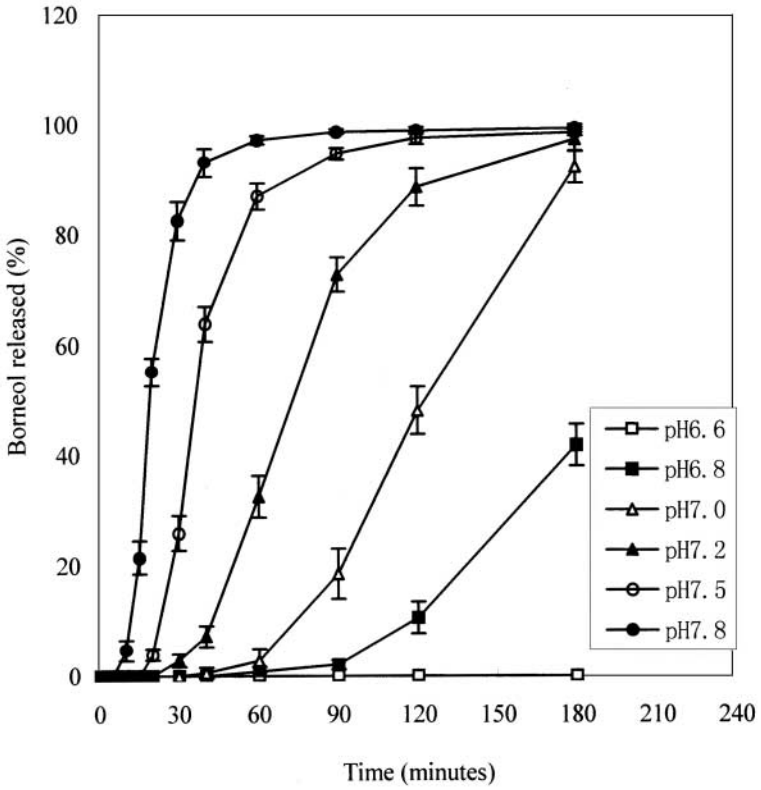

Figure 6. Effect of pH values of dissolution medium on the release of borneol from pellets coated with Eudragit L100–Eudragit S100 1:5 at 36% (w/w) coating load.

DISCUSSION

In vitro, the coating film was well resistant to gastric acid when the weight of Eudragit L30D-55 per square centimeter of surface area was over 3.93 mg/cm^2 (the coating load was 30%, w/w), and when the weight of Eudragit L100–Eudragit S100 1:5 per square centimeter of surface area was over 4.14 mg/cm^2 (the coating load was 36%, w/w). The results indicated that the technology used in the study is practicable.

It was proved that the pH of the dissolution medium had little effect on pellets coated with HPMC, but had significant effects on pellets coated with Eudragit L30D-55 and Eudragit L100–Eudragit S100 1:5. There was hardly any drug release at pH value lower than 5.5 for the pellets coated with Eudragit L30D-55 and at pH value lower than 6.8 for the pellets coated with Eudragit L100–Eudragit S100 1:5. But the drug release rate of pellets coated with Eudragit L30D-55 or Eudragit L100–Eudragit S100 1:5 was obviously different at various pH conditions when the pH was over the lowest pH values at which the coating film could be dissolved. This was because the dissolution rate of coating film was different at various pH conditions. The results are in agreement with those in previous reports.[21–23]

Since the pH value was 7.49 ± 0.46 in the small intestine, with that for a few individuals lower than 7.0, the pH value in the colon was 6.63 ± 0.67.[12,13] The pellets coated with only Eudragit S100 might come out intact in the feces, without releasing any drug in the GIT due to the coating film not being dissolved. To avoid this phenomenon, we selected Eudragit L100 and Eudragit S100 combinations 1:5 as film-forming material.

The design of this work was based on the idea that a novel sustained-release delivery system, which could gradient-release at different places of the GIT, would be developed through the use of the different pH values in the stomach, duodenum, jejunum, and ileum. The restriction factor for this kind of delivery

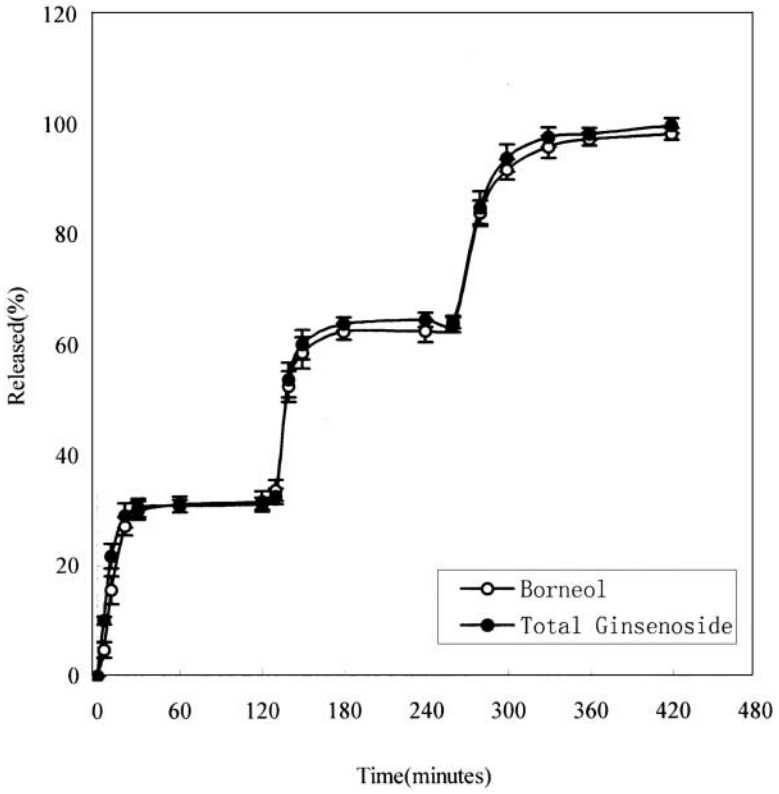

Figure 7. The release profiles of borneol and total ginsenoside from HPMSRC in the simulated gastrointestinal pH conditions.

system is the gastric emptying time. However, pellets of about 1 mm in diameter as an oral multiparticulate system can pass intact through the pylorous into the duodenum. After oral administration, the pellets can be distributed quickly in the stomach, and the gastric emptying of pellets in a fast state was a stochastic process. In a fed state, pellets can be widely distributed in food and then pass with chyle into the duodenum. Thus, the effects of gastric emptying on pellets were far less than on tablets. The transit time of the dosage forms in the small intestine was relatively stable, and little affected by food or the physical properties of the drug delivery system. As a consequence, it could be predicted that after oral administration the novel delivery system consisting of three kinds of pellets coated separately with HPMC, Eudragit L30D-55, and Eudragit L100–Eudragit S100 1:5 could sustainedly release drug after immediate release of a part of the drug, which would avoid the problem of the lag time of common sustained-release dosage forms in vivo.

The contents of muscone, cinnamic acid, and cinnamic aldehyde, etc., in heart-protecting musk pellets were so low that it was very difficult to determine their dissolution from pellets in vitro. The borneol was selected as the index of dissolution test because of its higher content. It was proved that in vitro the dissolution of borneol, muscone, cinnamic acid, and cinnamic aldehyde from the refined intermediate products had good correlations. It was presumed that the dissolution behaviors of the other lipophilic components were similar to that of borneol.

It was reported in many articles that the pH values in the stomach were in the range 1.2 to 5.0, the pH values in the duodenum, jejunum, and ileum were 6.63 ± 0.53, 7.41 ± 0.36, and 7.49 ± 0.46, respectively.[12,13] The average gastric emptying time of pellets was 2 hr or so, and the mean cecum arrival time of pellets was in the range 5–7 hr after oral administration.[16–19] Therefore the dissolution behavior of borneol from HPMSRC was tested at pH 1.2 for 2 hr, pH 6.6 for 2 hr, and then pH 7.5

for 3 hr successively, to mimic the gastrointestinal conditions.

Since the decomposition of ginsenoside would occur in 0.1 mol/L HCl,[27] phosphate buffer of pH 5.0 was used as dissolution medium of total ginsenoside of pellets coated with HPMC. From the dissolution of borneol it was found that the dissolution of HPMC film was little affected by the pH of the media. It was inferred that the total ginsenoside release from pellets in pH 5.0 or 1.2 would not be different. The release rate of total ginsenoside was a little faster than that of borneol because of the higher solubility of total ginsenoside in water. The results of the dissolution test in the simulated gastrointestinal pH conditions indicated that the dissolution of pH-dependent gradient-release pellets was dependent on the pH value of the dissolution medium. Therefore, the release of water-soluble total ginsenoside and lipophilic borneol was synchronous, except for a slight difference in the beginning. It was inferred that various original components of HPMSRC, though different in properties, could synchronously release while sustained-releasing.

CONCLUSIONS

Three kinds of coated pellets were prepared using HPMC and two methacrylic acid copolymer aqueous systems, Eudragit L30D-55 and Eudragit L100–Eudragit S100 combinations 1:5, as film-forming material, respectively. The results of dissolution in vitro demonstrated that the coating load and the pH of the dissolution medium had little effect on the release rate of drug from pellets coated with HPMC, but had a significant effect on the release rate of drug from pellets coated with Eudragit L30D-55 and Eudragit L100–Eudragit S100 combinations 1:5. The above three kinds of pellets were encapsulated in hard gelatin capsules at a certain ratio to obtain HPMSRC. In vitro, the above three kinds of pellets of HPMSRC could release drug in pH 1.2, 5.5, or above and 6.8 or above dissolution medium, respectively, and a pH-dependent gradient-release pattern was observed. According to the variance of pH and transit time of GIT, it was inferred that HPMSRC could sustained-release drug after immediate release of a part of the drug after oral administration, and various components with different properties in the HPMSRC could synchronously release while sustained-releasing. This complies with the organic whole concept of compound compatibility of traditional Chinese medicine.

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