In vitro Preparation and Evaluation of Sustained-Release Microcapsules of Salvianolic Acid

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Objective: This study aims to investigate the preparation of sustained-release microcapsules of salvianolic acid.

Methods: The stability of salvianolic acid microcapsules was improved, and the time of action was prolonged in the present study. This was prepared using the spray-drying method, with chitosan as the carrier. In the preparation process, the prescription and process were optimized by L9 (34) using an orthogonal design, with yield and drug loading as indexes, in order to obtain optimum conditions.

Results: The optimal process and prescription for the preparation of salvianolic acid microcapsules were found to be as follows: mass concentration of chitosan, 1.5%; mass ratio of salvianolic acid to chitosan, 1:3; inlet air temperature, 190°C; and peristaltic pump speed, 300 mL·h-1. The surface of the microcapsules was round, the drug loading was 25.99% ± 2.14%, the yield was 51.88% ± 2.84%, the entrapment efficiency was 86.21% ± 2.89%, and the average particle size was 105.6 ± 2.56 nm. The microcapsules in vitro had certain sustained release characteristics. The internally fitted first-order release model equation was ln(1-Q) = -0.236 t + 4.591 7, r = 0.920. In addition, the results of differential scanning calorimetry show that the properties of salvianolic acid were not changed by the microcapsules.

Conclusion: Sustained-release microcapsules of salvianolic acid can be successfully prepared by adopting marine polysaccharide as a carrier.

Keywords: salvianolic acid sustained-release microcapsule, marine polysaccharides, chitosan, Salvia miltiorrhiza, salvianolic acid B

Introduction
The dry root and rhizome1-3 of the plant Salvia miltiorrhiza Bge (of the Labiatae family) are often used to treat cardiovascular and cerebrovascular diseases.2,4,5 Modern pharmacological research has revealed that salvianolic acid B is one of the effective components of S. miltiorrhiza. This is a tetramer of caffeic acid compound, which is condensed by two-molecule tanshinol and one-molecule prolithospermic acid. However, its chemical properties are very unstable and easily degraded.6 Microcapsules are tiny capsules that encapsulate solid or liquid drugs, along with excipients that can improve the stability of the drugs and mask their unpleasant smells.7 As stable carriers, microcapsules are widely used in the preparation of chemical drugs; however, they are rarely used in traditional Chinese medicine. The purpose of this study was to apply microencapsulation technology to certain main
components of traditional Chinese medicine, so as to realize their potential as patent medicines. To this end, in the present study, salvianolic acid B was prepared into microcapsules using marine polysaccharide as a carrier.

**Methods**

**Materials and Instruments**

All materials used—salvianolic acid Bcontrol (National Institute for the Control of Pharmaceutical and Biological Products, Batch No. 110817-200605), salvianolic acid (salvianolic acid B: 58%, Xi’an Honson Biotechnology Co., Ltd., Batch no. 090926), chitosan (degree of deacetylation ≥ 95%, viscosity < 60 cp, Shandong AK Biotech Co., Ltd., Batch no. 090926), hydrochloric acid (Chongqing Chuanhong Chemical [Group] Co., Ltd., Chemical Reagent Factory), and other reagents—were analytically pure.

The instruments used were as follows: Agilent 1200SL RRLC (Agilent, USA), SD-1500 small spray dryer (Shanghai Wodi Technology Co., Ltd.), H-7500 transmission electron microscope (Japan Hitachi), S-3000N scanning electron microscope (Japan Hitachi), Zetasizer Nano ZS90 nanometer particle size and zeta potential analyzer (Malvern, UK), Spectrum One infrared spectrometer (Perkin-Elmer, USA), STA-449C differential scanning calorimeter (Netzsch, Germany), AW-200 electronic balance (Shimadzu, Japan), and ZRS-8G intelligent dissolution tester (Tianjin University Wireless Power Plant).

**Preparation of Salvianolic Acid Microcapsules**

Chitosan was precisely weighed and dissolved with 0.1 mol·L⁻¹ of hydrochloric acid to prepare solutions with different mass concentrations, and these were placed in standby. The salvianolic acid was dissolved into the chitosan solution and prepared into the solution, and sprayed according to a certain proportion. This was evenly stirred for spray drying after standing and removing the bubbles.

**Evaluation of Drug Loading**

Approximately 60 mg of microcapsule powder was precisely weighed and placed in a 25-mL flask. Hydrochloric acid was added for dissolution and constant volume. After ultrasound, the liquid was shaken, and 1.0 mL was transferred into a flask and diluted to scale with 0.1 mol·L⁻¹ of hydrochloric acid solution. Then, peak area A was determined. The drug mass concentration was calculated according to the standard curve equation, and drug loading was calculated according to the following formula: drug loading = drug content in microcapsules/total mass of microspheres × 100%.

**Determination of Yield**

The microcapsules in the receiving flask were collected using a spray dryer and weighed. The percentage of feed volume of the microcapsules, ie, the yield, was calculated. The calculation formula was yield = obtained microcapsule quality/total feed volume × 100%.

**Preparation Method**

Specificity tests. Controls were prepared as follows: salvianolic acid B controls of 0.00771 g were accurately weighed, dissolved with 75% ethanol, and diluted to 25 mL to obtain the final product. For the salvianolic acid extract solution, salvianolic acid extract of 0.02065 g was accurately weighed; again, this was dissolved with 75% ethanol and diluted to 25 mL to obtain the final product. For the blank solution, 0.02589 g of chitosan was precisely weighed and dissolved in water, and diluted to 25 mL to obtain the final product. The sample solution was prepared by precisely weighing 0.06081 g of microcapsules, which were dispersed with a small amount of absolute ethyl alcohol; 0.2 mol/L of hydrochloric acid was added to dissolve and dilute this to 25 mL.

Sample assay methods. From each of the above-mentioned solutions, 20 μL was injected into the liquid chromatograph for determination.

**Results**

**Sample Specificity Chromatogram**

As stated above, 20 μL of the sample solution was injected into the liquid chromatograph. The results, presented in Figure 1, reveal that chitosan was completely separated from the main drug and had no interference with the determination of the drug. Furthermore, this was strongly specific.

**Establishment of Standard Curves**

Next, 1.59 mg of salvianolic acid B control was accurately weighed and dissolved with 75% methanol solution to a constant volume of 25 mL, in order to prepare a solution of 63.60 μg·mL⁻¹. Each 0.25, 0.50, 0.75, 1.00, 1.50, and 2.00 mL of solution was taken into a 10-mL volumetric flask, and 75% methanol solution was used to maintain a constant volume. The above series of standard
Figure 1 Specificity of the chromatogram.
solutions was filtered via a 0.45 µm millipore filter. This was tested based on chromatographic conditions in Sample Specificity Chromatogram. The sample injection was 20 µL. Peak area A was measured as the longitudinal coordinate, while linear regression was conducted for the concentration according to the regression equation: \( A = 1.765 \times 0.230 + 6, r^2 = 0.9998 \). The results show that salvianolic acid B has a good linear relationship between 1.59 and 12.72 µg mL\(^{-1}\).

**Precision Test and Recovery Test**

The prepared mass concentrations were 1.59, 6.36, and 12.72 µg mL\(^{-1}\). The salvianolic acid B control solution was measured three times a day. The relative standard deviation (RSD) was calculated as 1.73%, 2.16%, and 0.93%, respectively, within the day. Measurements were taken at day 1, 2, and 3, and the calculated RSD was 0.93%, 1.45%, and 1.96%, respectively, within the day.

Quantities of 1.12, 2.23, and 3.03 mg of salvianolic acid B controls were accurately weighed, and blank microcapsules were added according to the prescription dosage. These quantities were dissolved with 0.1 mol·L\(^{-1}\) of hydrochloric acid to prepare mass concentrations of 1.59, 6.36, and 12.72 µg mL\(^{-1}\), respectively, in order to test peak area A. The results indicate that the average recovery rate was 99.62%, 102.36%, and 99.31%, respectively.

**Table 1** Drug Loading Caused by Different Ratio of Drug to Chitosan

| Ratio of Drugs to Chitosan | Dosage of Salvianolic Acid (g) | Dosage of Chitosan (g) | 0.1 mol/L HCl (mL) | Drug Loading (%) | Yield [% (g)] |
|---------------------------|-------------------------------|-----------------------|-------------------|-----------------|-------------|
| 1:1                       | 50.00                         | 50.00                 | 5000              | 50.00           | 45.55 (68.33) |
| 1:2                       | 50.00                         | 100.00                | 1000              | 33.33           | 47.34 (94.68) |
| 1:3                       | 50.00                         | 150.00                | 15000             | 25.00           | 44.18 (110.45) |
| 1:4                       | 50.00                         | 200.00                | 20000             |                 |             |

**Table 2** Drug Loading Caused by Different Concentration of Chitosan

| Concentration of Chitosan (%) | Dosage of Salvianolic Acid (g) | Dosage of Chitosan (g) | 0.1 mol/L HCl (mL) | Drug Loading (%) | Yield [% (g)] |
|------------------------------|-------------------------------|-----------------------|-------------------|-----------------|-------------|
| 0.5                          | 50.00                         | 150.00                | 30000             | 33.33           | 31.41 (62.81) |
| 0.8                          | 50.00                         | 150.00                | 18750             | 33.33           | 41.16 (82.32) |
| 1.0                          | 50.00                         | 150.00                | 15000             | 33.33           | 47.34 (94.68) |
| 1.5                          | 50.00                         | 150.00                | 10000             |                 |             |

**Single-Factor Test for the Selection of the Spray Drying Process**

A series of microcapsules was prepared according to the method in Preparation of Salvianolic Acid Microcapsules, based on drug-to-chitosan ratios of 1:1, 1:2, 1:3, and 1:4. The results reveal that when the ratio of drug to chitosan was 1:4, the drug loading and yield of the microcapsules were low, because the ratio of drug to chitosan was too small. When the ratio of drug to chitosan was 1:1, the salvianolic acid extract could not be completely dissolved in the chitosan. Therefore, the drug-to-chitosan ratio should be between 1:2 and 1:3 (Table 1).

A series of microcapsules was prepared using chitosan mass concentrations of 0.5%, 0.8%, 1.0%, and 1.5%, according to the method in Preparation of Salvianolic Acid Microcapsules. The experimental results show that the mass concentration of chitosan should be controlled within the range of 0.8% to 1.5%. This is because when the viscosity of the chitosan solution is too high, the nozzle can easily become blocked, preventing the spray process from being carried out normally; however, when the concentration is too low (0.5% or less), the microcapsule powder is mainly deposited in the shunt flask, resulting in a lower yield (Table 2).

According to the preparation method in Preparation of Salvianolic Acid Microcapsules, a series of microcapsules was prepared with peristaltic pump velocities of 300, 400, 500, 600, and 700 mL·h\(^{-1}\). During the experiment, it was
found that when the speed of the peristaltic pump was 700 mL·h⁻¹, obvious water droplets formed in the spray dryer, indicating that the spray droplets were not completely dry, and the yield was low. When the speed decreased to 600 mL·h⁻¹, the powder was still slightly wet. As 300 mL·h⁻¹ is the minimum rotation speed of the instrument, the acceptable range of the peristaltic pump speed was thus determined to be between 300 and 500 mL·h⁻¹.

According to the preparation method in Preparation of Salvianolic Acid Microcapsules, a series of microcapsules was prepared at inlet air temperatures of 150°C, 160°C, 170°C, 180°C, 190°C, and 200°C. In the course of the experiment, it was found that when the inlet air temperature was below 170°C, the droplets could not be dried, indicating that the inlet air temperature cannot be lower than 170°C.

According to the results of single-factor investigation, the main influencing factors are as follows: the drug-to-chitosan ratio (A), the mass concentration of chitosan (B), the speed of the peristaltic pump (C), and the air inlet temperature (D). In order to optimize the prescription and process for preparing microcapsules, an orthogonal test was carried out. The trial protocol is presented in Table 3. Drug loading and yield were taken as the comprehensive evaluation indexes. The weight coefficients were all 0.5. The results are presented in Tables 3 and 4.

According to the range analysis, the order of each influencing factor for the salvianolic acid microcapsules was as follows: C > D > B > A. The final optimal process and prescription for the preparation of salvianolic acid microcapsules are A₃B₃C₁D₃, i.e., salvianolic acid-to-chitosan ratio = 1:3, mass concentration of chitosan = 1.5%, peristaltic pump speed = 300 mL·h⁻¹, and inlet air temperature = 190°C.

### Proof Test

The optimal process and prescription conditions were obtained on the basis of the orthogonal test results. Three batches of salvianolic acid microcapsules were prepared. The results, presented in Table 5, show that the process has good reproducibility. Although the results for the microcapsules prepared according to the optimal process and prescription conditions (A₃B₃C₁D₃) were close to the results for orthogonal test 6 (A₂B₃C₁D₂), in view of the higher proportion of the capsule, and the notion that the higher the rate of encapsulation, the higher the inlet temperature, and the less likely the nozzle is to block, the optimal process and prescription conditions A₃B₃C₁D₃ were finally selected for the preparation of the microcapsules.

#### Quality Evaluation

**Morphology of the Microcapsules**

The microcapsule sample is a slightly yellow powder, with no bad smell, and good dispersibility and stability. The surface morphology of the microcapsules was observed by scanning electron microscope (SEM) (Figure 2). The results indicate that the microcapsule was round, with a smooth and clean surface, and did not adhere.

**Particle Diameter**

An appropriate number of salvianolic acid microcapsules were taken and diluted with water. The particle size and zeta potential were determined using a Zetasizer laser particle analyzer, as illustrated in Figure 3. As shown in

| No. | A  | B (%) | C (mL·h⁻¹) | D (°C) |
|-----|----|-------|------------|-------|
| 1   | 1  | 0.2   | 300        | 170   |
| 2   | 1  | 0.25  | 400        | 180   |
| 3   | 1  | 0.3   | 500        | 190   |

| No. | Drug Loading | Average Value (%) | RSD (%) | Yield (%) | Average Value (%) | RSD (%) |
|-----|--------------|-------------------|---------|-----------|-------------------|---------|
| 1   | 25.29        | 25.99             | 2.14    | 50.56     | 51.31             | 2.84    |
| 2   | 25.69        | 26.98             | 2.14    | 50.56     | 51.31             | 2.84    |
| 3   | 26.98        | 29.30             | 2.14    | 50.56     | 51.31             | 2.84    |

**Table 4 The Results of the Orthogonal Test (n=3)**

**Table 5 The Results of Confirmatory Experiment**
the figure, the average particle size of the microcapsules was 105.63 ± 2.56 nm, the polydispersity index was 0.411 ± 0.023, and the zeta potential was 47.71 ± 1.36 mV. The results indicate that the particle size of the microcapsule was small and the system was stable, but the particle size distribution was not sufficiently uniform; this needs to be improved.

Differential Scanning Calorimetry (DSC)

The salvianolic acid microcapsules, salvianolic acid extract, chitosan, and physical mixture were determined by DSC. The weight of the sample was approximately 6 mg. The test temperature was 0°C to 450°C, and the temperature rose by 10°C min⁻¹ (the results are shown in Figure 4). These results show that salvianolic acid and salvianolic acid embedded in microspheres have similar absorption peaks, of 250.562°C and 241.53°C, respectively; there was no significant difference between the two groups. The results indicate that the microcapsules did not change the properties of salvianolic acid.

Preliminary Study on the Release Properties of Microcapsules in vitro

Methodological Study on Dissolution in vitro

The release rate was determined using the XD release method in Appendix II of the Chinese Pharmacopoeia 2015. In the pilot experiment, the optimal release medium
was selected. Water, 0.01 mol·L⁻¹ hydrochloric acid, phosphate buffer solution pH 6.8, phosphate buffer solution pH 7.4, and phosphate buffer solution pH 4.5 were each used to determine the cumulative release degree. The presence of white turbidity was observed in the dissolution cup for the microcapsules in water, phosphate buffer solution pH 6.8, and phosphate buffer pH 7.4, possibly due to the insolubility of the chitosan. ⁵⁻¹⁰ In addition, the microcapsule release was too fast in 0.01 mol·L⁻¹ hydrochloric acid, and the salvianolic acid was unstable under these conditions. ¹¹⁻¹⁴ Therefore, the optimal release medium for the microcapsules was identified as phosphate buffer pH 4.5.

**Preparation of Release Medium**

For the acetic–sodium acetate buffer solution (pH 4.5), 18 g of sodium acetate was taken, 98 mL of acetic acid was added, and this was diluted with water to 1,000 mL to obtain the final product.

**Preparation of a Standard Curve**

Next, 2.25 mg of salvianolic acid B control was accurately weighed and dissolved with 75% methanol solution to a constant volume of 25 mL, in order to prepare a solution of 63.60 μg·mL⁻¹. Each 0.1, 0.2, 0.4, 0.8, 1.60, and 3.2 mL of solution was taken into a 10-mL volumetric flask, and a 75% methanol solution was used to maintain a constant volume. The above series of standard solutions was filtered using a 0.45-μm Millipore filter. This was tested based on chromatographic conditions in Sample Specificity Chromatogram. The sample injection was 20 μL. Peak area A was measured as the longitudinal coordinate, and linear regression was conducted for the concentration according to the regression equation: \( A = 2.1570 \times 0.1854, r^2 = 0.9995 \). The results reveal that salvianolic acid B has a good linear relationship between 1.02 and 32.64 μg·mL⁻¹.

**Determination of Sample Release in vitro**

According to the Second Method “Device” of General Rule 0931 of the Pharmacopoeia of the People’s Republic of China 2015, 900 mL of each of the above five release media was used as the release medium, at a temperature of 37.0°C ± 0.5°C and a rotating speed of 100 r·min⁻¹. Each 20 mg of prepared salvianolic acid powder and microcapsule was precisely weighed and placed in a large cup. The sampling times were 30, 60, 120, 180, and 240 minutes, and the sampling quantity was 5 mL. The initial filter was discarded, and the sample was injected (the same amount of isothermal medium was added at the same time). The release degree was calculated according to the standard curve. The cumulative release curve was plotted (Figure 5), and drug release curve fitting was carried out. The

![Differential thermal scanning diagram](https://www.dovepress.com/)

**Figure 4** Differential thermal scanning diagram. (A) Physical mixture of salvianolic acid extract and chitosan; (B) salvianolic acid extract; (C) chitosan; (D) microcapsule.
results, presented in Table 6, reveal that the first-order drug release model can explain the drug release behavior better than the zero-order drug release model and the Higuchi equation. In the release medium, the cumulative release rate of salvianolic acid powder was 100% within 30 minutes, whereas in the salvianolic acid microcapsules prepared by spray drying it was 74.62% ± 3.15%, indicating that the microcapsules had a certain sustained release effect.

Discussion

In the present study, salvianolic acid microcapsules were prepared by spray drying; this is convenient to operate, easy to control, uses a non–organic solvent, and is suitable for industrial production. In addition, the microcapsules have a round form and good fluidity. The amount of drug loading can reach up to 25.99%, laying a foundation for the development of microcapsules of the solid preparation of salvianolic acid.

The results of the drug release in vitro reveal that the release amount reached 45.3% at the beginning of 30 minutes. Furthermore, there was a sudden release effect, which may be mainly due to the rapid dissolution of microcrystals attached to the surface of the microcapsule. Additionally, there may be micropores on the surface of the microcapsule, through which the release medium can quickly enter the microcapsule and dissolve the drug to form a higher or even saturated concentration. According to the concentration difference, the drug molecules were rapidly diffused from the micropores to create a sudden release. The release was relatively slow within 30 to 240 minutes due to the water absorption and swelling of chitosan, and the micropore diameter was reduced or even disappeared.15–17 When the micropore channel was closed, subsequent drug release could only take place slowly by diffusion through the skeleton, or through the degradation of chitosan.18–20 After 240 minutes, the cumulative release rate decreased, possibly due to the instability and accelerated degradation of salvianolic acid. However, release conditions in vitro are quite different from those in vivo; further in vivo experiments are therefore necessary.

Limitations remain in the present study. First, this study concerned an in vitro experiment. Due to the great difference between in vitro and in vivo conditions, the findings need to be further confirmed through in vivo experiments. Second, although it is known that salvianolic acid B is one of the effective components of *S. miltiorrhiza*, its specific mechanism remains unclear, and should be further investigated.

Conclusions

The results of this study show that sustained-release microcapsules of salvianolic acid can be successfully prepared using marine polysaccharide as the carrier. However, due to the great
difference between in vitro and in vivo conditions, this needs to be further confirmed through in vivo experiments.

Disclosure
The authors declare no conflict of interest in this work.

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