A Novel Method to Mask the Bitter Taste of Berberine Hydrochloride: Powder Surface Modification

Hong Jiang, Dingkun Zhang, Jing He, Xue Han, Junzhi Lin, Yang Lan, Xi Xiong, Lingying Yu, Ming Yang, Li Han

Abstract

Background: Berberine hydrochloride (BH) is widely used as a nonprescription drug to treat diarrhea without drug resistance and side effects worldwide. However, its drastic bitterness affects patient compliance severely. Hence, it is essential to mask the bitter taste of BH. Objective: Powder surface modification technology is attempted to mask the bitterness of BH through changing the surface properties in vibromill. The purpose of this study was to apply this technology to mask the bitterness of BH and improve the patient compliance. Materials and Methods: Initially, to prepare the modifier-BH composites, some parameters were optimized, including type of modifiers, ratio between BH and modifiers, and composite time. Then, the contact angles, scanning electron microscopy, and infrared (IR) spectroscopy were utilized to evaluate the microstructure of composites. Moreover, electronic tongue measurement, animal performance test, and bitterness evaluation methods were applied to evaluate the masking effect. Results: Based on the results of bitter taste evaluations, mannitol was chosen as the best modifier, and the optimal ratio of BH and mannitol was 6:4 with grinding together for 2 min in vibromill. For the composites prepared by this process, the IR spectroscopy and surface properties were similar with that of mannitol, and the microstructure was also demonstrated that small particles of mannitol successfully coated on the surface of BH. Special structure of the composites decreased the contact area between BH and external media and finally inhibited the bitterness. This effect was confirmed by three different kinds of methods. Conclusion: Our study provides a novel method to mask the bitter taste of drugs. It will be of great interest to pharmaceutical experts and pharmacists.

Key words: Berberine hydrochloride, bitter taste masking, powder surface modification, surface property, vibromill

Summary

- Powder surface modification, a novel and different from previous technology, is used to prepare modifier-berberine hydrochloride composites to mask the bitter taste of BH
- Electronic tongue measurement, animal performance test, human sensory test, and chemical evaluation method were simultaneously applied to evaluate the masking effect
- A novel method to mask the bitter taste of drugs was provided

INTRODUCTION

Diarrhea is a common disease in the world, which negatively affects living quality, reduces work productivity, and spends quite a considerable expense. The most lethal risk is high mortality, especially for children <5 years of age. Clostridium difficile infection (CDI) is the most common cause of infectious diarrhea in health-care settings. In the past, vancomycin was a preferred antibiotic for treating CDI. However, its severe renal toxicity and ototoxicity limited the application. Berberine hydrochloride (BH), an isoquinoline alkaloid obtained from the roots, rhizomes, and stem bark of natural herbs such as Coptidis Rhizoma, Phellodendri Chinensis Cortex, and Berberidis Radix, is another commonly used drug in the treatment of diarrhea. It could not only significantly inhibit the recurrence of CDI but also do not produce the drug resistance and side effects. In addition, BH possesses anti-inflammatory activity and anticancer efficacies. Therefore, BH owns promising application prospect and important research value. To inhibit the bitterness of BH, quite a few methods were developed, including cyclodextrin inclusion and solid dispersion. However, these approaches often needed to use a large number of accessories.
Tablet coating was the most commonly used method. Although it was recognized as the most effective method, some deficiencies were unable to avoid. From the point of view of preparation technology, tablet coating process was not easy to accurately control, especially for the coating thickness and uniformity, and tablets adhesion. Moreover, for the sugar coating, the dosage of coating materials was generally larger, even beyond 70% of the weight of plain tablets. From the point of view of clinical medication, coated tablets were particularly unsuitable for the patients with difficulty in swallowing, especially for the children and elder people. These patients still needed to crush the tablets before administration, and tablet coating could not meet their medication demands. Therefore, it is essential to find a novel method to mask the bitter taste of BH.

As we known, the combination of bitter drugs and its receptors in the oral cavity produces bitter taste.\(^{[18]}\) It is an important approach to mask the bitter taste by slowing down the release rate of drug and reducing the concentration of free molecules in the saliva.\(^{[19,20]}\) Powder surface modification is an important method in the preparation of materials. It can change the surface properties of powders using physical, chemical, or mechanical methods and improve the new properties and application functions.\(^{[21]}\) The modification methods in existence are done in blend machine, high-speed mill, fluidized bed, and vibromill. In recent years, this method has been introduced into the pharmaceutical technology to achieve some special purpose, include increasing the solubility of the insoluble drugs,\(^{[22,23]}\) changing surface wettability,\(^{[24]}\) decreasing the hygroscopicity,\(^{[25]}\) and improving the flowability,\(^{[26,27]}\) and compressibility.\(^{[28,29]}\) Powder surface modification was first adopted to mask the bitter taste of BH. It was obviously different from traditional tablet coating method and was especially suitable for children and elderly patients with difficulty in swallowing and needed to crush the tablets. Moreover, this method could replace the original tablet coating process and significantly shorten the production process of BH tablets.

In this study, powder surface modification was used to prepare the modifier-BH composites to mask the bitter taste of BH. First, bitterness evaluation methods were established to screen the preparation parameters of the composites, including the types of modifiers, ratio of BH and modifiers, and composite time. Then, the physical properties were characterized by contact angles (CAs), scanning electron microscopy (SEM), and infrared (IR) spectroscopy to study the relationship between the modifiers and BH in the composites. Moreover, electronic tongue measurement, animal preference test, and bitterness evaluation methods were applied to evaluate the masking effect of the modifier-BH composites. These results manifested that powder surface modification could be used to mask the bitter taste of BH and improve the oral compliance. Eventually, new ideas and methods could be provided for the masking of other bitter drugs.

**MATERIALS AND METHODS**

**Ethics statement**

This study was conducted in strict accordance with the recommendations of the Guidelines for the Care and Use of Laboratory Animals of the Ministry of Science and Technology of China. The protocol and designs were approved by the ethical committee of Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (Approval ID: 2014KL-016). Participants were received "written informed consent" on the study’s purpose and of their right to keep information confidential. Written consent was obtained from all participants or their guardians.

**Materials and reagents**

BH (purity 98%, No. 140901) was purchased from Sichuan Yuxin Medicine Co., Ltd. (Sichuan, China). BH reference substance (purity <98%, No. 110713-200911) was purchased from the National Institutes for Food and Drug Control. Mannitol and β-cyclodextrin were obtained from Chengdu Kelong Chemical Reagent Company (Sichuan, China). Hypromellose was purchased from Anhui Shanhe Pharmaceutical Excipients Co., Ltd. Acetonitrile of high-performance liquid chromatography (HPLC)-grade was purchased from Shanghai Ludu Chemical Reagent Company (Shanghai, China). All other reagents were analytical grade and available locally. Water was ultrapure water.

Male Sprague–Dawley rats weighing 180–220 g were purchased from the Institute of Laboratory Animals of Sichuan Provincial People’s Hospital (Permit No. SCXK [Chuan] 2013–2015, Chengdu, China) and were employed for the study as per the ethical regulations of Affiliated Hospital of Chengdu University of Traditional Chinese Medicine.

Animals were housed in plastic cages under standard conditions (22°C ± 1.5°C, under a 12-hour light–dark cycle with lights on at 8:00 am, and food and water provided ad libitum). Rats were made adapt to the laboratory conditions for at least 1 week before data collection. All experiments were performed during the light phase of the light–dark cycle. All possible steps were taken to avoid animals' suffering at any stage of the experiments.

**Establishment of human sensory test**

**Preparation of standard solution**

Bitterness could be divided into five levels. Each level was given a certain range of intensity of bitterness.\(^{[30]}\) The description method is shown in Table 1. According to the classification of the bitter taste, the concentration of BH standard solution was, respectively, 0, 0.027, 0.134, 0.269, and 1.345 mmol/L.

**Preparation of the sample solutions**

An amount of 0.3724 g BH was accurately weighed and dissolved in 1 L purified water with ultrasonic treatment. The solution was diluted to 0.001, 0.0025, 0.01, 0.025, 0.1, 0.25, 0.5, and 1 mmol/L. Moreover, the samples were independently marked as S1, S2, S3, S4, S5, S6, S7, and S8.

**Human sensory evaluation**

Twenty well-trained and healthy volunteers (ten males and ten females, age 18–28 years) participated in the sensory evaluation. Volunteers were selected from the graduate students at Chengdu University of Traditional Chinese Medicine. Informed consent was obtained before initiating the study. During training sessions, volunteers were trained with different concentrations of standard solutions (0, 0.027, 0.134, 0.269, and 1.345 mmol/L) to accustom them to evaluation scales and intensity of bitter taste of the standard solutions. A sample of about 10 mL was applied on the upper surface of the tongue and lasted for 15 s. Between each test interval, each volunteer was asked to wash his/her mouth well with distilled water to no bitterness. Volunteers were given a break approximately 20–30 min between each session.\(^{[31]}\) The same operation was done to evaluate eight sample solutions. The volunteers according to their own taste, combining with the bitter taste of BH, determined the bitter taste of samples and gave the specific intensity of bitterness.

**Screening model, evaluation, and verification**

In this paper, the logarithmic model \((f_1)\) (1) and the Weibull relationship model\(^{[32]}\) \((f_2)\) (2) were tested to establish the relationship between the intensity of bitter taste and concentration according to the results of human sensory evaluation. The relationships of the two models were as follows:

Logarithmic model: \(I_g = f_{(1)} = \alpha \ln (c) + b\) \(\quad (1)\)

Weibull relationship model: \(I_g = f_{(2)} = 5.5 \times (1 - e^{-m c})\) \(\quad (2)\)

where \(c\) represented concentration, \(\alpha\), \(\beta\), and \(m\) were undetermined parameters, \(e\) referred to the base of natural logarithms, and 5.5 was...
the maximum of intensity of bitterness. According to the method of "programming solver," the appropriate initial values were selected. The intensity of bitterness of different concentration range could be calculated according to the established model to replace the human sensory evaluation. Hence, the concentration of BH was measured using HPLC in this paper. The BH was directly compressed into tablets (the content of BH was about 0.3 g) with the diameter of 13 mm. Then, the tablets were placed in a 50 mL thermostat water bath (37°C ± 0.5°C) to dissolve for 15 s and taken out. The solutions would be filtered through 0.45-μm membrane filters. The filtrate could then be used directly for HPLC analysis. HPLC was performed on a Shimadzu chromatographic system (LC-10ATvp, Shimadzu, Japan); a Welchrom C_{18} column (4.6 mm × 250 mm, 5 μm, Shanghai Yuanxu Material Technology Co., Ltd., China) was used. Acetonitrile-water (1:1, v/v) was used as the mobile phase at a flow rate of 1 mL/min. The ultraviolet detection was conducted at 265 nm. The column temperature was 25°C, and the injection volume was 10 μL. Then, combining with the model, the intensity of the solution could be obtained.

### Establishment of chemical evaluation method

The bitter taste of samples was produced by the combination of BH and relative bitter receptors in oral cavity. With the concentration of BH increasing, the combined probability between BH and receptors would grow and the bitterness would be stronger. Therefore, we would make the samples dissolved in water to simulate and measure the content of BH in oral cavity to evaluate the bitter taste of BH.

The BH was directly compressed into tablets (the content of BH was about 0.3 g) with the diameter of 13 mm. Then, the tablets were placed in a 50 mL thermostat water bath (37°C ± 0.5°C) to dissolve for 15 s and taken out. The solutions would be filtered through 0.45-μm membrane filters. The filtrate could then be used directly for HPLC analysis. The operating conditions of HPLC were same as given above.

### The preparation process of berberine hydrochloride composites

#### Preparation of composites

The BH and modifiers were dried in a vacuum drying chamber to a moisture content of 3% or less. An amount of 400 g modifiers were first added to SYFM-II vibromill (Songyue, China). Then, 600 g BH powder was added to the vibration mill. By smashing and blending, modifiers with small particle size would coat on the surface of the BH with large particle size under the action of mechanical force. Eventually, the modifier-BH composites were obtained. The operation parameters of vibromill were as follows: grinding media were stainless steel column, the filling rate was 80%, and the amplitude was 5.5 mm.

#### Selection of modifiers type

Based on the preliminary study of the powder properties of common excipients, mannitol, hyprolose, and β-cyclodextrin were selected as the modifiers to mask the bitterness of BH in this study. The ratio of BH and modifiers was 6:4 and composite time was 2 min. The masking effect was assessed using the established bitterness evaluation methods above.

### Selection of ratio of berberine hydrochloride and modifiers

The ratio of the modifiers and the drugs would directly affect the amount of modifiers coated on the surface of the drugs. Therefore, three kinds of composites were prepared according to the different ratio of BH and the chosen modifiers (mannitol) (7:3, 6.5:3.5, and 6:4) in this paper, and the composite time was 2 min. Moreover, bitterness evaluation methods were used to select the best proportion.

### Selection of composite time

Based on the method mentioned above, BH and modifiers (mannitol) were ground in vibromill, and the ratio was 6:4. Moreover, the composites were, respectively, sampled at 1, 2, and 3 min. Then, three kinds of composites were evaluated and scored according to the bitterness evaluation methods.

### Verification of preparation technology

Based on the optimal parameters determined by bitterness evaluation methods, the prepared modifier-BH composites powder was tested.

### Preparation of mixtures

Based on the type of modifiers, proportion, and composite time as determined above, BH and modifiers were accurately weighed according to the ratio and then grounded and mixed in a mortar. After passing through a sieve for further mixing, the physical mixture powder was finally obtained.

### Preparation of tablets

Based on the optimized parameters (modifiers type, ratio of BH and modifiers, and composite time), modifiers tablets, BH tablets, composites tablets, and mixture tablets were directly compressed using a TR-D8 multi-functional tablet machine with pressure of 60 N. Each tablet had a diameter of 13 mm and weighed about 0.4 g.

### Physical characterization

#### Contact angles[24]

The size of CAs was mainly related to the composition and distribution of surface elements. CAs were an important index to reflect the surface properties of the material.[24] In this paper, CAs of the samples were measured to determine whether the composites were successfully prepared.

CAs of samples (modifiers tablets, BH tablets, composites tablets, and mixture tablets) were measured by a video optical CA system (OCA20, Data Physics, Germany) at ambient temperature. Water was used as test liquid. The rate was controlled at 0.5 μL/s. Each sample was measured five times, and average CAs were recorded.

### Scanning electron microscopy

Take a small amount of modifiers, BH powder, composites powder, and mixture powder as samples. Samples were coated with a thin layer of gold using the E-1010 ion sputtering device (Hitachi, Japan). The shape and surface morphology were observed under an environmental scanning electron microscope (JSM-7500F, Japan).
**Infrared spectroscopy**

IR spectra were recorded on a Cary 630 Fourier transform infrared spectrometer (Agilent Technologies Inc., United States). 200 mg of potassium bromide and 1 mg of sample were ground and mixed in an agate mortar until a uniform mixture was generated. Then, tablets were prepared at 10 N of pressure for 5 min and fixed in circular sample loop.

**Taste-masking test**

**Electronic tongue measurement**

Electronic tongue could gather a large number of chemical information about drug solutions through seven sensors and had been developed to accurately evaluate the bitter taste of BH. The taste-masking effect of samples was evaluated by a sensor-based system, ASTREE II Electronic Tongue System (Alpha MOS, Toulouse, France) equipped with seven liquid cross-selective sensors (ZZ, AB, GA, BB, CA, DA, and JE). The response intensity of each sensor was measured with an Ag/AgCl reference electrode. The potentiometric differences between each coated sensor and the reference electrode contribute to the intensity value of the measured samples. Solution samples were prepared according to the following protocol; modifier tablets, BH tablets, composite tablets, and mixture tablets were placed in a 50 mL thermostat water bath (37°C ± 0.5°C) to simulate the release of drugs in oral cavity. After dissolving for 15 s, these tablets were taken out, and each solution would be filtered through 0.45-μm membrane filters. Then, the filtrate was directly analyzed by electronic tongue. The acquisition time was fixed at 120 s. Each sample was replicated 10 times, and only the 8th–10th datasets were taken into account for the statistical treatment. Sensors were rinsed with distilled water between each measurement. Measured data were recorded and analyzed by AlphaSoft Software (Alpha MOS, Toulouse, France).

**Animal preference test**

Taste preferences were assessed using a brief-access test with the following samples, presented in the order listed: BH tablets, composite tablets, and mixture tablets. They were placed in a 50 mL thermostat water bath (37°C ± 0.5°C) to dissolve for 15 s and taken out as samples solution. In the test, rats were deprived of water for 24 h and then made to lick bottles containing water, and licking activity observed in 5 min. Number of times the rat licks the bottle in 5 min was counted and analyzed by electronic tongue. The acquisition time was fixed at 120 s. Each sample was replicated 10 times, and only the 8th–10th datasets were taken into account for the statistical treatment. Sensors were rinsed with distilled water between each measurement. Measured data were recorded and analyzed by AlphaSoft Software (Alpha MOS, Toulouse, France).

**Human sensory evaluation**

Three samples (BH powder, mixture, and composites) were evaluated and scored according to the selected model and criteria which were described above.

**Chemical evaluation**

Three samples (BH powder, mixture, and composites) were determined by chemical evaluation.

**Date analysis**

Statistical analysis was carried out using SPSS 19.0 software (SPSS, Inc., Chicago, IL, USA). Differences were considered statistically significant at \( P < 0.05 \). Data are reported as mean ± standard deviation and as individual values in the figures.

**RESULTS**

**Human sensory evaluation**

The intensity of bitter taste of BH is shown in Figure 1a. The line was the logarithm of concentration. The results showed that the correlation between intensity of bitterness and concentration was positive. Moreover, the final models were as follows:

\[
I_p = f_{(x)} = 0.6718\ln (c) + 5.0741, R^2 = 0.9866
\]

\[
I_p = f_{(x)} = 5.5 \times e^{-0.3968 (x-0.0013)^{0.0001}}, R^2 = 0.9986
\]

The fitting curves of the two models are shown in Figure 1b. Based on the logistic equation fitting, the degree of correlation of Weibull model was higher than the logarithmic model. Thus, Weibull model \( f(x) \) was chosen to evaluate samples.

**Chemical evaluation**

In chemical evaluation, by simulating the release amount of BH, the content of BH could be measured to reflect the level of bitterness generated in the oral cavity. Therefore, the releases of BH in 2 min could be used as evaluation indexes of bitter taste.

**Preparation of composites**

**Selection of modifiers type**

The results of the modifiers are shown in Figure 2a. Different modifiers displayed different intensity of bitterness and release amount of BH. It indicated that mannitol and β-cyclodextrin both reduced the bitter taste of BH, while hyprolose could enhance the bitterness of BH. Mannitol and β-cyclodextrin were successfully coated on the surface of BH, which could slow the release of BH. However, hyprolose with good expansibility could accelerate the disintegration of tablets and increase the release of BH. Therefore, mannitol-BH composites and β-cyclodextrin-BH composites reduced the bitter taste of BH; the hyprolose enhanced the bitterness of BH. In addition, the masking effect of mannitol to BH was better than β-cyclodextrin. In addition, mannitol had a little sweet taste and good stability. Therefore, mannitol was chosen as the best modifier in this paper.

**Selection of ratio of berberine hydrochloride and modifiers**

The results of proportion are shown in Figure 2b. It demonstrated that proportion had different masking effects on BH. The taste of composites could be obviously improved as the increasing of modifier proportion. Moreover, when the ratio of BH and modifiers was low, the surface of BH could not be completely coated with modifiers. Hence, the ratio of BH and mannitol was determined to be 6:4.

**Selection of composite time**

The results of composite time are shown in Figure 2c. It was showed that composite time had an important influence on the composites structure and could affect the bitterness level. When composite time was 1 min, modifiers was not completely coated on the surface of the BH. When composite time was 2 min, the bitter taste of composites was lowest. Hence, the bitterness of composites was slightly bitterer than 2 min. However, when it was 3 min, the formed composite structures would be destroyed with time increasing. Therefore, the composite time was ensured at 2 min. After a serial of single-factor experiments, the preparation technology of composites was determined to be “the drugs and modifiers (mannitol) proportion of 6:4, with composite time of 2 min.”
Physical characterization

Contact angles

Table 2 shows the results of CAs. It was manifested that CAs of composites were close to mannitol. However, CAs of mixture were similar to that of the BH original powder. It was proved that the surface properties of composites were similar to mannitol, while the mixture mainly displayed the surface properties of BH. Hence, it indicated that mannitol successfully coated on the surface of the BH under the action of mechanical force. In addition, the result verified that drugs and modifiers were not physically mixed in the vibromill.

Scanning electron microscopy

The microstructures are shown in Figure 3. Mannitol displayed relatively regular appearance with similar-globose shape, but its particle size was heterogeneous. BH powder was irregular square in shape with obvious crystal structure. Further, its size was more than ten times that of mannitol. In the mixture, the surface of BH powder was coated by a small amount of modifiers, and most of BH powder could be obviously seen. However, the microstructures of the composites could be evidently found that BH powder was coated by a large number of small diameter materials perfectly. It declared that mannitol-BH composites were successfully prepared and provided a foundation structure for reducing bitterness of BH.
Table 2: Determined results of contact angle (±s, n=3)

| Samples   | Contact angle (°) |
|-----------|-------------------|
| Mannitol  | 16.0±0.62**       |
| BH        | 23.8±0.32**       |
| Mixture   | 20.1±0.55**       |
| Composite | 16.8±0.46**       |

Versus mannitol, **P<0.01; versus BH, *P<0.01. BH: Berberine hydrochloride

Infrared spectroscopy

The IR spectroscopy is performed as shown in Figure 4. The composites had similar absorption with mannitol at 630, 699, 1018, 1081, 1271, 1420, 3233, 3243, 3283, 3287, 3322, 3336, 3346, 3365, and 3396 cm⁻¹ but had similar absorption with BH only at 1271, 1361, 1505, and 3407 cm⁻¹. In general, absorption curve of the composites was similar with that of mannitol. However, absorption curve of the mixture was both similar with that of BH powder and mannitol. In addition, there were some differences between the composites and mixture. The result showed that surface characteristics of composites were more similar to mannitol. Further, the mixture possessed the properties of BH powder and mannitol.

Taste-masking test

Electronic tongue measurement

Figure 5a shows the result of electronic tongue measurement. The analysis model was positive as the information of PC1 and PC2 containing included 98.3% of all information. The three samples were detected as being different from each other. In more details, the Euclidean distance between mixture and BH powder was nearer than that between composites and BH powder. The mixture possessed more similar bitterness with BH powder than composites. Therefore, it indicated that bitter taste of BH in the composites was effectively masked.

Animal preference test

Animal preference test [Figure 5b] showed that the preference index of composites was higher than mixture and was obviously higher than BH powder at the same concentrations. The preference index of up to 70% was obtained for composites indicating that the solution did not exhibit very bad taste. However, the preference index of BH powder was 34%, proving that the powder possessed strong bitterness. It proved that the mannitol-BH composites were less bitter than the BH powder.

Human sensory test and chemical evaluation

The results of bitter taste evaluation are shown in Figure 5c. The composites had the lowest intensity of bitterness according to the Weibull model. Meanwhile, compared with the BH powder and mixture, the release amount of BH in the composites was also the lowest. It demonstrated that composites could inhibit the bitter taste by reducing the release of BH.

To sum up, combining with the results of taste-masking test, each result demonstrated that the composites could reduce the bitterness of BH. Human sensory test could truly reflect the bitterness of BH, while human had subjective and could not distinguish the subtle differences between different samples. However, electronic tongue measurement had high sensitivity and distinguishing ability so that it could make up for the deficiency of human sensory evaluation. Hence, the simultaneous application of these methods could increase the credibility of these results.

DISCUSSION

When the powder surface modification was applied, the particle size of modifiers was much smaller than that of drugs and generally did not exceed 1/10 of the former. Under this condition, the modifiers will automatically adsorbed on the surface of the drugs due to the spontaneous reduction of the Gibbs free energy of the system, which is the thermodynamic basis for the powder surface modification. After the modifier firmly coated on the surface of the drug, the modifier weakens the bitter taste of the drug by slowing down the release of the drug. In the past research, powder surface modification has not been used to mask the bitter taste. In the research, powder surface modification is used to mask the bitter taste of BH. Through the optimization of a series of process parameters, the mannitol-BH composites were successfully prepared. According to the results of bitterness evaluation, the bitterness of the composites was significantly reduced compared with the original powder and the mixture. In addition, combining with the results of physical characterization, the composites had a special structure which mannitol coated on the surface of BH.

CONCLUSION

In the research, the mannitol-BH composites were successfully prepared by the powder surface modification, and process parameters were optimized. The physical structure of the composites was characterized...
by CAs, SEM, and IR spectroscopy. Moreover, the composites were less bitter than the BH powder and mixture according to the results of electronic tongue measurement, animal performance test, and bitterness evaluation methods. Considering all the results together, it demonstrated that powder surface modification was useful and outstanding for masking the bitter taste of BH.

Acknowledgements

Sample preparation was supported by Senior Engineer Guo Zhi-ping (Sichuan Houde Medical technology Co., LTD) and Ph. D. Wang Xiao-ping (Jiangxi University of TCM). This research was supported by grants from the National Natural Science Foundation of China (No. 81403115, 81274098).

Financial support and sponsorship

This work was financially supported by the National Natural Science Foundation of China (Grant No. 81403115, 81274098).

Conflicts of interest

There are no conflicts of interest.

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