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ORIGINAL ARTICLE

A Novel Strategy for Bitter Taste Masking of Gankeshuangqing Dispersible Tablets Based on Particle Coating Technology

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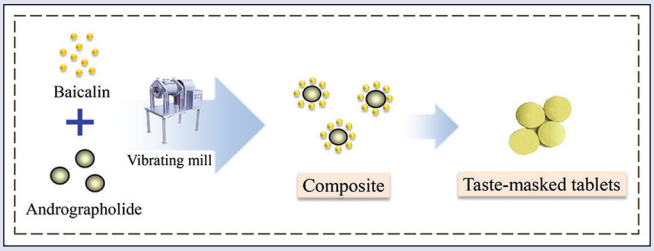
ABSTRACT

Background: Currently, acute upper respiratory tract infections (AURTIs) are increasingly becoming a significant health burden. Gankeshuangqing dispersible tablets (GKSQDT) which have a good effect on treating AURTIs. GKSQDT is composed of baicalin and andrographolide. However, its severe bitterness limits application of patients. Due to the addition of plentiful accessories, common masking methods are unsuitable for GKSQDT. It is thus necessary to develop a new masking method. **Materials and Methods:** The Previous study showed that baicalin was less bitter than andrographolide. Thus, particle coating technology was adapted to prepare composite particles that baicalin coated on the surface of andrographolide to decrease bitterness. Initially, particle size of baicalin and coating time of composite was investigated to prepare composite. Then, scanning electron microscopy, wettability, and infrared (IR) spectrogram were used to characterize the microstructure of composite. Furthermore, electronic tongue test, animal preference experiment, and human sensory test were applied to evaluate the masking effect. **Results:** To produce composite, baicalin should be ground in vibromill for 6 min. Then, andrographolide fine powder was added to grind together for 6 min. Contact angle of composite was smaller than mixture, and more similar to baicalin. Other physical characterization including microstructure, wettability, and IR also suggested that andrographolide was successfully coated by baicalin superfine. Furthermore, taste-masking test indicated taste-masked tablets was less bitter than original tablets. **Conclusion:** The study indicated that particle coating technology can be used for taste masking of GKSQDT without adding other substance. Moreover, it provides a new strategy of taste masking for national medicine.

Key words: Animal preference experiment, bitter taste making, electronic tongue test, ganke shuangqing dispersible tablets, particle coating technology

SUMMARY

- A new strategy to mask bitterness without adding any other substance based on coating technology was provided
- The masking effect was confirmed by electronic tongue test, animal preference experiment and human sensory test.



Abbreviations used: AURTIs: Acute Upper Respiratory Tract Infections; GSQDT: Gankeshuangqing Dispersible Tablets; IR: Infrared Spectrogram; LHPC: Low-substituted Hydroxypropyl Cellulose; CAs: Contact Angles; FTIR: Fourier Transform Infrared Spectra.

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INTRODUCTION

Currently, acute upper respiratory tract infections (AURTIs) are increasingly becoming a significant health burden, especially among children.[1] Gankeshuangqing dispersible tablets (GKSQDT) have a good effect on treating AURTIs. Clinical trial found that it could obviously relieve coughing, reduce sputum secretion, shorten treatment course, and decrease antibiotics consumption.[2] Overuse of antibiotics may lead to resistance, increased cost, and increased incidence of adverse effects.[3,4] The bioactive components baicalin and andrographolide in the formulation are confirmed to own antibacterial activity.[5-8] Especially, andrographolide, honored as natural antibiotics, has a good treatment effect for the viral infection.[7]

The GKSQDT formulation is composed of 50% of baicalin, 12.5% of andrographolide, and 23% of $CaSO_4$, 11.5% of low-substituted hydroxypropyl cellulose (L-HPC), 4% of SiO_2.[9] The source of andrographolide, *Andrographis paniculata*, is known as king of bitters. It is generally known that taste is extremely important for the efficacy of preparations. Severe bitter taste, caused by andrographolide,[10] imposes restrictions on the oral compliance, and widespread application of GKSQDT. With the rising number of elderly people and health burden caused by AURTIs in children, the administration of drugs to pediatric and elderly patients is becoming more important and should be more considered.[11] Hence, to ensure patient compliance and promote the application of GKSQDT, the problem of bitter taste needs to be settled.

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The reason of bitter taste could be perceived by human is as follows. First, drug and bitter taste receptors on taste cells are combined to produce stimulations in oral cavity. Moreover, the stimulations shoot the gustation center in cerebral central region and are integrated by nerve center.[12-14] Based on the formation mechanism of bitter taste, there are three kinds of commonly used masking approaches. One way is through adding sweet taste substances, flavors, or effervescent agents to interfere with the perception of bitter drugs. Commonly used accessories include sucralose, aspartame, orange, mint, tartaric acid, and sodium bicarbonate. Another way is slowing down or stopping drug release in oral cavity, including polymer coating, hot-melt extrusion, complexation (adding cyclodextrins or ion exchange resins), modification of solubility of drug (adding magnesium aluminum silicate), and spray-drying.[15-20] The third way is preventing the combination of G-protein coupled receptors and bitters through bitterness blocking agent, such as adenosine monophosphate, lipoproteins, and phospholipids.[21,22] The common point of these methods needs to add other substances on the basis of original prescription.[23,24] However, the proportion of baicalin and andrographolide in GKSQDT is as high as 62.5%. Thus, the amount of accessories is limited. Moreover, oral dispersible tablets are intended to dissolve and/or disintegrate rapidly in the mouth.[25] It is thus difficult to mask bitter taste using above methods for GKSQDT.

Currently, particle coating technology is mainly used in materials science and pharmaceutical industry, including drug layering, modified release coating, physical and chemical protection, esthetic purposes, and taste masking, enhanced identification of drugs.[26] Particle coating technology utilizes external force to combine several drugs or excipients particles to form composite according to certain structural models to change property of drug.[27] Among them, the most commonly used is core-shell structure model.[28] That is, materials with relatively large particle size (1–200 nm) form a core and these core particles are mechanically and orderly coated with superfine particles forming a single particle coating structure.[28] Taking the compositions of GKSQDT into account, an idea was come up to mask bitter taste. Whether can we use less bitter baicalin to coat on the surface of much bitter andrographolide? After all, blocking the contact of bitters is benefit for decreasing the bitter level.

In this paper, particle coating technology was adopted to prepare baicalin-andrographolide composite to mask bitter taste of GKSQDT. Moreover, coating time of composite was screened by human sensory evaluation. To confirm the successful preparation of composite, the microstructure, wettability, and infrared (IR) spectrogram of baicalin, andrographolide, mixture, and composite were characterized. Moreover, to measure the masking effect of particle coating technology for GKSQDT, electronic tongue test, animal preference experiment, and human sensory test were produced. The method was displayed in Figure 1. It showed that particle coating technology can be used to mask bitter taste of GKSQDT and improve the oral compliance without adding any other substance.

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 experimental 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

Baicalin (purity 80%, No. 100102) and andrographolide (purity 99%, No. 120812) were purchased from Sichuan Yuxin Medicine Co., Ltd., (Sichuan, China). $CaSO_4$ (No. 20100908), SiO_2 of pharmaceutical grade (No. 20110813), and ethanol (No. 20110703) were purchased from Chengdu Kelong Chemical Reagent Co., Ltd., (Sichuan, China). L-HPC of pharmaceutical grade (No. 20101027) was obtained from Shanghai Houcheng chemical Co., Ltd.(Shanghai, China). Water was purified using a Milli-Q water purification system (Millipore, Bedford, MA, USA). All other chemicals used were of analytical grade and available locally.

Sample preparation

Preparation of mixture

Baicalin and andrographolide were dried for 6 h at 60°C to make content of moisture <5%. Dried baicalin and andrographolide were ground to mix evenly as a proportion of 4:1 based on the prescription design.

Preparation of composite

Dried baicalin was first crushed to superfine powder. Then, it was ground with normal andrographolide for appropriate time as a proportion of 4:1 to make baicalin coated on andrographolide based on the prescription design.

Crushing laws of baicalin

For smaller fine particles, various surface forces (microscopic force) and force associated with the surface are more important than mass forces (macroscopic force) in particle motion. Therefore, intermolecular forces play a major role in the composite process of herbal medicine composite. From this, drugs should be crushed to a suitable particle size to carry out particle design. 300 g of baicalin was grinded in an SYFM-8II micronizing pharmaceutical vibrating mill (Jinan Beili Inc., China). About 10 g of baicalin was sampled, respectively, at 2, 4, 6, 8, 10 min $d_{0.5}$ of these samples were measured to observe the variation with time using an MS2000 particle size analyzer (Malvern Inc., Worcestershire, UK.). $d_{0.5}$ represents the number of particles smaller than a particular particle size accounts for 50% of total particles. Particle size gets smaller as $d_{0.5}$ is smaller.

Coating time of composite

Three hundred grams of baicalin particles and 75 g of andrographolide were ground together in vibration mill. Moreover, 10 g was respectively sampled at 3, 6, and 9 min. Then, three composite particles were evaluated and scored according to the follow method and criteria.

Human sensory test

Twenty well-trained and healthy volunteers (half men and women, age 22–28) participated in the sensory evaluation.[29] Volunteers were selected from 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 andrographolide solutions (0.5, 5, 50, 500 μg/mL) to accustom them to evaluation scales and intensity of bitter taste of the standard solutions. A drop of approximately 10 mL of each solution was applied on the upper surface of tongue. Between each test interval, the mouth was rinsed well to no bitterness with distilled water. Volunteers were given a break between each session. Then, the test solution was spitted out. The bitterness level of reference solutions was scored and described in Table 1.

In the human sensory evaluation of taste-masking effect of baicalin-andrographolide composite, each volunteer contained 50 mg of sample at the root of tongue near the middle position for 30 s. Then, gargle for 5–10

times to no bitterness in the mouth using distilled water and informed the bitter level of sample.[30] After 20 min, the next sample was tasted. Volunteers were asked to give scores on a scale of 1–4.[30] The taste aggregate score S was calculated as S = 1 × N1 + 2 × N2 + 3 × N3 + 4 × N4 (N1 + N2 + N3 + N4 = 20 volunteers). The smaller total point was; the lower bitterness was.

Physical characterization

Scanning electron microscopy

Take a little baicalin, andrographolide, mixture, and composite on the sample stage with conductive glue fixing, and spray with gold-plated membrane by an E-1010 ion sputter (Hitachi, Japan). Then, the shape and surface morphology was observed with a JSM-7500F scanning electron microscopy (JEOL Ltd., Japan).

Contact angles

Contact angles (CAs) of samples were measured at ambient temperature on an OCA 20 video optical CA system (Dataphysics Inc., Germany). Four kinds of sample were compressed each about 0.2 g into tablets with pressure between 50 N and 60 N. The tablets had a diameter of 10 mm. Water was used as test liquid. 50 μL of water was needed each time, and the rate was controlled at 0.3 μL/s. The moment that droplets come into contact with tablets instantly was as start time. After repeated experiments early, it was known that CA tends to be stable about 1 min and this CA was as measurement result. Every sample was measured 5 times.

Infrared spectra

IR spectra were recorded on a Vertex 70 FT-IR spectrometer (Bruker Optics Inc., Germany). 40 mg of KBr and 1 mg of sample were ground and mixed in an agate mortar. Then, tablets were prepared at 10 N of pressure for 5 min and fixed in circular sample loop.

Taste-masking test

Electronic tongue measurement

The taste-masking effect of samples was evaluated by a sensor-based system, ASTREE II electronic tongue system (Alpha M.O.S., 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.[31] Sample solutions were prepared according to the following protocol: Baicalin, andrographolide, original tablets, and taste-masked tablets were accurately weighed 0.1 g and respectively dissolved into 100 mL of distilled water (andrographolide was dissolved into 40% ethanol). Each solution was then filtered through 0.45 μm nylon membrane filters. The acquisition time was fixed at 120 s.[32] Each sample was replicated 10 times, and only the 8th to 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 experiment

Male Sprague-Dawley (SD) rats weighing 180–200 g were obtained from the Institute of Laboratory Animals of Sichuan Provincial People' 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 (23.5°C ± 1.5°C, under a 12-h light–dark cycle with lights on at 8:00 am, food and water provided *ad libitum*). Rats were adapted to laboratory conditions for at least 1 week before data collection. All experiments were performed during the light phase of the light–dark cycle. All

Table 1: Description and scores of bitterness of andrographolide solutions

Concentration (μg/mL)	Taste description	Score
0.5	Little tasteless or slightly bitter taste	1
5	Bitterness can accept	2
50	Bitter, but barely acceptable	3
500	Very bitter, unacceptable	4

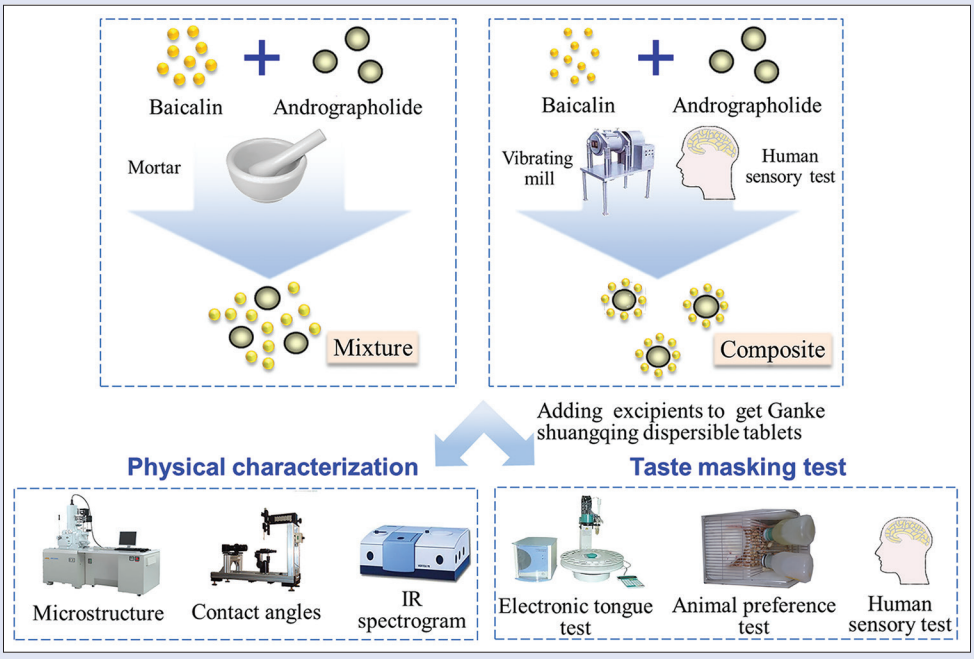

Figure 1: The experimental flow chart

possible steps were taken to avoid animals' suffering at any stage of the experiments.

Taste preferences were assessed using ascending concentration series of 48-h two-bottle choice test[33] with the following samples, presented in the order listed: Original tablets and taste-masked tablets (1, 5, 10, 20 mg/mL). Totally,16 rats were randomly classified into two groups: The original tablets group and the taste-masked tablets group with 8 rats in each group. In each test series, the rats first received two drinking tubes containing distilled water for 48 h, and then a choice between distilled water and ascending concentrations of samples, with each test lasting 48 h. The positions of two drinking tubes were switched every 24 h. Intakes from each tube were obtained by recording the level of fluid (on a volumetric scale to the nearest 0.1 mL) at the beginning and end of each 48-h test. Total fluid intakes were obtained by adding together the intakes from both drinking tubes. Preference scores were calculated as intake of the solution divided by total intake. When preference index >50%, it indicates that the rats are fond of the sample. Otherwise, it suggests that the rats dislike the sample.

Human sensory test

The procedure of this test was similar to "Coting time of composite". In the sensory evaluation, 1 tablet of sample approximately 0.3 g was contained at the root of tongue near the middle position for 30 s while the sample was GKSQDT and taste-masked tablets.[34] And a drop of approximately 10 mL of sample was applied on the upper surface of tongue while the sample was water suspension of GKSQDT and taste-masked tablets at a concentration of 2 tablets/100 mL. Every volunteer tastes each sample 1 time to avoid fatigue.

Statistical analysis

Data are reported as mean ± standard deviation (SD) and as individual values in the figures. Differences were considered statistically significant at $P < 0.05$. Statistical analyses were performed using SPSS 19.0 package (SPSS, Inc., Chicago, IL, USA).

RESULTS

Preparation of composite

The varying pattern of baicalin between $d_{0.5}$ and grinding time was shown in Figure 2a. It showed that particle size decreased sharply during 0–6 min. However, then, particles trended to reunite, and the particle size had a slight increase. This maybe result in surface ions of particles owned a larger proportion after ultrafine grind. It enhanced the surface activity and gravity between particles. On the other hand, in ultrafine grinding process, there was a high static of particle surface. It easily led to attract and aggregate in the colliding process. Hence, grinding time should be controlled at 6 min as particle size was smaller and would not be agglomerated.

A human sensory evaluation was performed to measure bitterness intensity in all samples to ensure the coating time of composite. The final result was shown in Figure 2b. It could be known that composite was less bitter than mixture, and the coating time affected bitterness level. When coating time was 3 min, part of andrographolide was uncoated, and bitterness was still evident. Composite coated at 9 min were slightly bitterer than 6 min as some composite was destroyed. Hence, the final coating time was determined at 6 min.

Physical characterization

From Figure 3a, the microstructure of sample, baicalin was mostly irregular strip and wide lamellar. Andrographolide was massive and relatively regular. The mixture consisted of baicalin and andrographolide (4:1) and was observed only a small part of baicalin coated andrographolide surface. Composite was observed that andrographolide was closely coated by baicalin. It declared baicalin-andrographolide composite was successfully prepared and provided a foundation structure to reduce the bitterness of andrographolide.

It could be known from Figure 3b that the CA of mixture and composite were between baicalin and andrographolide; however, the CA of composite was smaller than mixture. It indicated andrographolide was successfully coated by baicalin.

The Fourier transform infrared (FTIR) spectra [Figure 3c] showed several intense bands in the region between 4000 cm^{-1} and 400 cm^{-1}. FTIR spectra of baicalin showed OH stretchings at 3600 cm^{-1} and 3500 cm^{-1}, a C=O stretching absorption at 1684 cm^{-1}, and C=C stretching at 1609 cm^{-1}, 1573 cm^{-1}, 1551 cm^{-1}, and 1496 cm^{-1}. Peaks at 1066 cm^{-1} indicate the stretching of C-O-C glycosidic bond.[35,36] The FTIR spectrum of andrographolide showed a characteristic OH stretching at 3395 cm^{-1}, a C=O absorption band at 1674 cm^{-1}, and a C-OH bending at 1295 cm^{-1}, a C-OH stretching at 1112 cm^{-1}. Exocyclic methylene group was observed at 900 cm^{-1}. The free OH attached to the lactone ring demonstrated a band at 3386 cm^{-1}.[37,38] Moreover, absorption peak of baicalin at 3000 cm^{-1} (C-H stretching) was single, but andrographolide was bimodal. Mixture had a similar absorption with andrographolide at 3000 cm^{-1}, 1674 cm^{-1}, 1295 cm^{-1}, 1112 cm^{-1}, and 900 cm^{-1}. However, composite had a similar absorption with baicalin at 1609 cm^{-1}, 1573 cm^{-1}, 1551 cm^{-1}, and 1066 cm^{-1}. IR spectrogram showed that surface characteristics of composite were more similar to baicalin, not andrographolide.

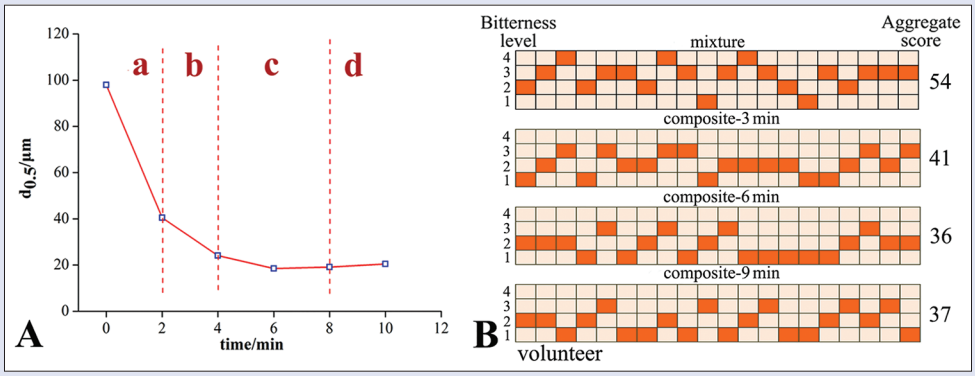

Figure 2: Preparation of composite particles. (A) Varying pattern between $d_{0.5}$ of baicalin and grinding time. (a) Rapidly changing, (b) slowly changing, (c) balance, (d) inverse crushing. (B) Sensory evaluation for composite of different grind time

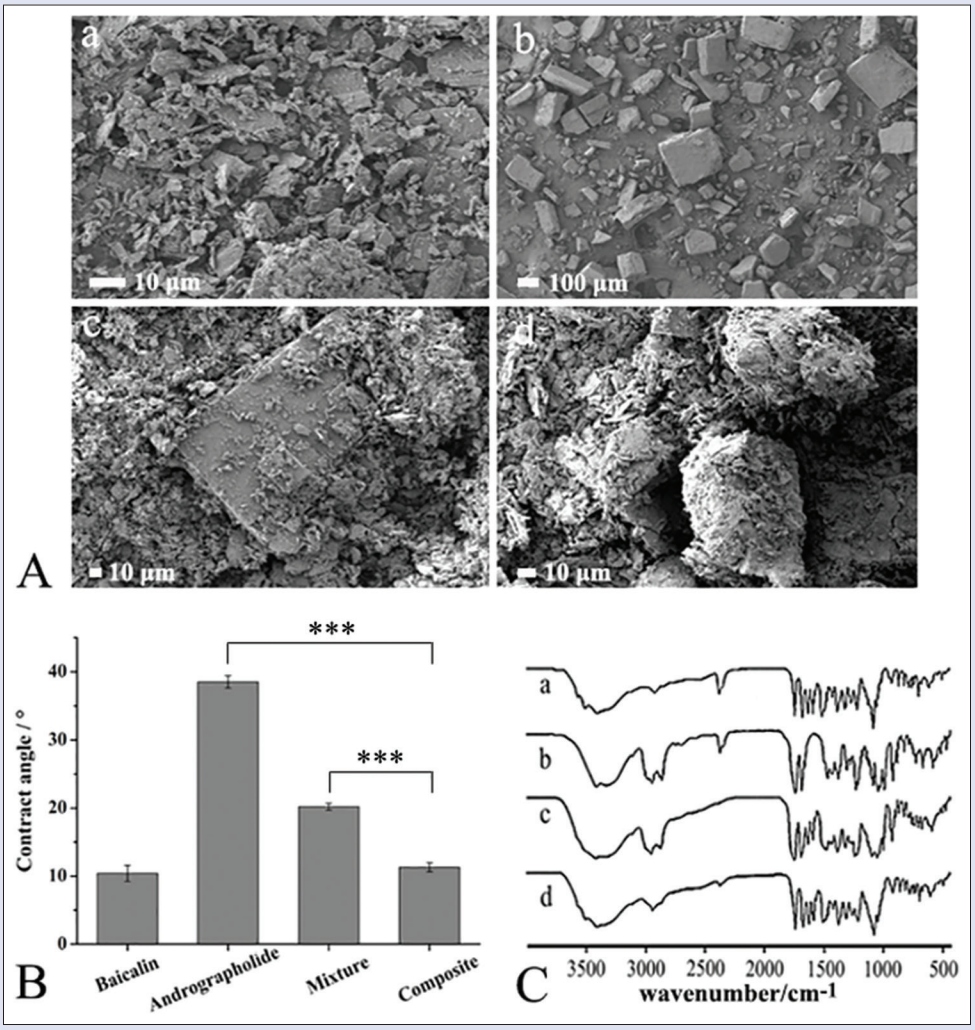

Figure 3: Physical characterization of samples. (A) Scanning electron microscopy of baicalin ×1000 (a), scanning electron microscopy of andrographolide ×50 (b), scanning electron microscopy of mixture ×300 (c), and scanning electron microscopy of composites ×500 (d). (B) Determination results of contact angle (n = 5, °), ***P < 0.001, effect of composite within andrographolide and mixture. (C) Infrared spectra of baicalin (a), andrographolide (b), mixture (c), and composite (d)

Taste-masking test

The testing samples were shown in Figure 4a. Principal component analysis was used for statistical analysis of e-tongue sensor data. From Figure 4b, it showed that the Euclidean distance between original tablets and baicalin was smaller than that between taste-masked tablets and baicalin. Moreover, Euclidean distance between original tablets and andrographolide was bigger than that between taste-masked tablets and andrographolide. Hence, it may indicate that taste-masked tablets were less bitter than original tablets.

Animal preference experiment proved the inference. Two-bottle choice test [Figure 4c] showed that the preference index of taste-masked tablets was higher than original tablets at 4 different concentrations. Both groups showed concentration-dependent decreases in intakes and preferences. Hence, when higher concentrations of drug solutions were offered to rats, they were not acceptable.

Volunteers gave scores for bitterness level of original and taste-masked tablets and suspensions. As a whole, the bitterness level of taste-masked samples was lower than original samples. Combined with the results of electronic tongue and rats, it indicated that the taste-masking effect of particle coating technology for GKSQDT was well.

DISCUSSION AND CONCLUSION

In this paper, particle coating technology was adopted to prepare baicalin-andrographolide composite to mask bitter taste of GKSQDT not adding other substance. The crushing rule of baicalin was first investigated to select appropriate particle size as shell particles. The result showed that the crush time should be maintained at 6 min and particle size of baicalin was more appropriate. Moreover, the coating time of andrographolide and baicalin was determined at 6 min as this composite was least bitter evaluated by volunteers. Further, physical characterizations containing microstructure, wettability, and IR of baicalin, andrographolide, mixture, and composite were produced. It indicated that the baicalin-andrographolide composite was prepared successfully and it was different from mixture. Moreover, to measure the masking effect of particle coating technology for GKSQDT, electronic tongue test, animal preference experiment, and human sensory test were produced. The results in the paper showed that taste-masked tablets were less bitter than original tablets. It indicated that it was feasible to adapt particle coating technology to mask the bitterness of drug without adding any other substance, especially for many national medicine which was consisted of big portion of crude drug.

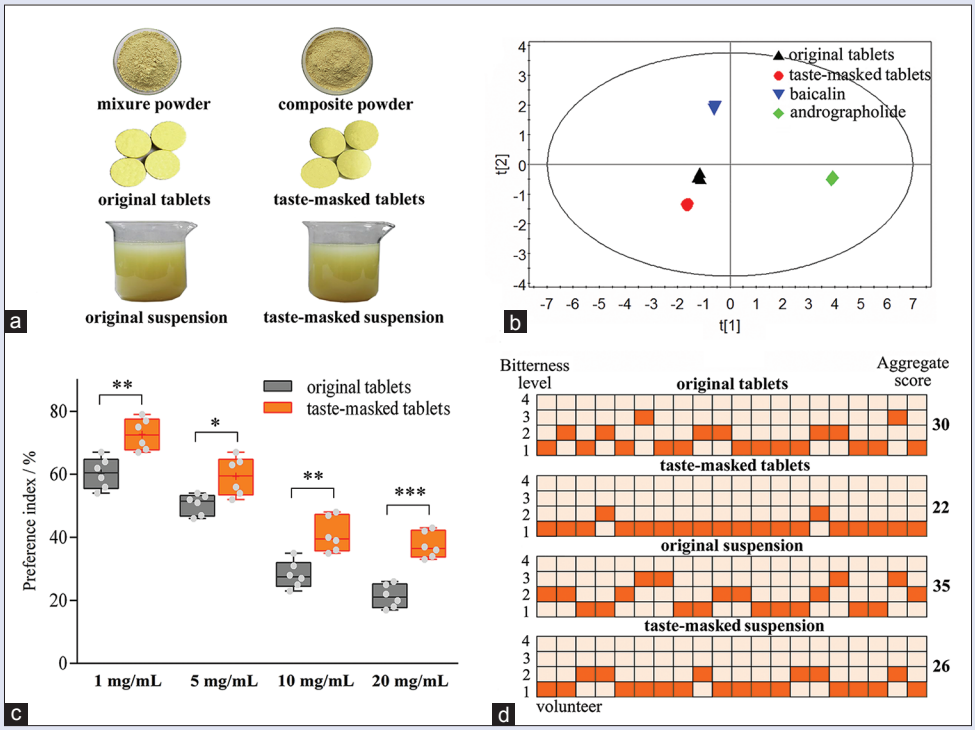

Figure 4: Taste-masking measurement. (a) Gankeshuangqing dispersible tablet and taste-masking tablet and their water suspensions (4 tablets/100 mL water). (b) Result of electronic tongue test (at a concentration of 1 mg/mL). (c) Result of animal preference experiment ($n = 8$, the test sample was suspended in water). (d) Scores of sample evaluated by 20 volunteers

Particle coating technology adapted for taste masking in the paper only needed an instrument, micronizing pharmaceutical vibrating mill. It was common used in pharmaceutical factory. Therefore, it was feasible and economical to apply this strategy for taste masking.

The tablets form was acceptable for adults to avoid the unpleasant taste but was problematic for children. Many children could not or would not swallow solid dose forms.[39] However, dispersible tablets were divided into two types. One was dispersed in stomach while the other in glass. For children, GKSQDT could be taken in suspension form as Figure 4c and d showing that taste-masking suspension was more pleasant than original suspension.

Most national medicine tasted bitter more or less. However, there was just a small portion that tasted extremely bitter. Most of the national medicine could be received by patients. Andrographolide tasted extremely bitter while baicalin tasted little bitter. It was successful to mask bitter taste using baicalin to coat andrographolide in this paper. Therefore, the masking method using less bitter drug or excipient to coat bitterer drug to achieve core-shell structure could be used in other bitter formulations without adding other substance. However, the pharmacological effects of taste-masked GKSQDT were still unknown and how big change of pharmacological effects after taste masking was also unknown. Therefore, pharmacodynamics will be researched in further study.

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Conflicts of interest

There are no conflicts of interest.

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