Study on Preparation Technology and Quality Standard of Acne Granules

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Pharmaceut Fronts 2024;6:e305–e314.

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Abstract

The study aimed to optimize the preparation process of acne granules and establish their quality standards. In this work, the extraction process of Chinese herbal extract was optimized by the amount of water added, the number of decoction, the extraction time, and the soaking time with extraction yield as an evaluation index. The indexes of the acne granules such as molding rate, dissolvability, angle of repose, moisture content, and ease of preparation were evaluated. Thin-layer chromatography (TLC) was used to identify *Salviae*, *Scutellaria baicalensis*, and Indigowoad Leaf. High-performance liquid chromatography (HPLC) was used to determine the baicalin content in the granules. Based on orthogonal and single-factor experiments, the optimized extraction process of the prescription of nine medicinal materials was as follows: soaked in cold water for 2 hours, boiled three times, decocted with eight times the amount of water for 1.5 hours for the first time, and six times the amount of water for 1 hour for the second and third times. The combined extracts were concentrated to a relative density of 1.30 to 1.40 (20–30°C), and mixed evenly according to the mass ratio of extract to excipient 1:5, and dextrin: powdered sugar = 1:3. The mixture was granulated, dried, prepared into granules, and the acne granules were formed at a molding rate of 95.52% and a critical relative humidity of 82%. The spots in TLC were clear and easy to identify. The HPLC result showed that the content of baicalin was not less than 1.0 mg/g. The study provides a valuable reference for the production and preparation of the granules through optimization of the wet process and the excipient dosage. Furthermore, the established TLC method for the identification and the HPLC method for baicalin quantification laid the foundation for the quality control of the preparation in future studies.

Keywords

- acne granules
- orthogonal experiment
- extraction technology
- wet granulation
- quality standard

Introduction

Acne is one of the most common chronic inflammatory hair follicle sebaceous gland diseases,[1] mainly manifested as acne, pustules, nodules, and seborrhea, with a high clinical incidence, low cure rate, and repeated attacks, affecting the appearance of the patient and causing a great psychological burden.[2,3] Epidemiologic studies reveal that 80 to 90% of adolescents suffer from this disease.[4,5] According to traditional Chinese medicine (TCM) theory, acne is mainly caused by the accumulation of fever in the lungs and stomach,[6] which easily occurs as a result of eating too much greasy food and sweets in the daily diet. Therefore, clearing the heat in the lungs and purging may be a way to treat this disease.

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received
February 18, 2024
accepted
July 30, 2024
article published online
September 3, 2024

DOI https://doi.org/10.1055/s-0044-1789234.
ISSN 2628-5088.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

The acne granule is a prescription prepared by the experience of Ruikang Cai, Director of the Dermatology, Department of Air Force Medical Center. Furthermore, it is based on the famous prescription "Pipa Qingfei Decoction" by Guangsheng Qi, a famous doctor in the Qing Dynasty, and has been used in military hospitals for many years.[7] Granules prepared by modern technology are convenient for patients to carry. The acne granules are composed of nine TCMs, which have the efficacy of clearing heat and cooling blood, drying dampness, and detoxifying, and are used to treat acne or pimples. In more than 20 years of clinical application, the acne granules have had a good therapeutic effect on acne, especially for pimples with blood heat. At present, the preliminary formulation process of granules has been formed, and the tentative daily dosage is 12 g. In this work, the extraction process of the acne granules was investigated, the preparation process of the acne granules was optimized, and quality was evaluated, which lay the foundation for the process of the acne granules in the future.

Materials and Methods

Instruments and Experimental Materials

Loquat leave, *Santalum album* L., *Rehmannia glutinosa* Libosch., Tree Peony Bark, *Radix Paeoniae Rubra*, *Radix Salviae*, *Scutellaria baicalensis* Georgi, Indigowoad Leaf, and raw licorice slices were purchased from Bei Jing Qian Cao Traditional Chinese Medicine (Beijing, China). *Radix Salviae* (batch number 120923-201816), baicalin (batch number 110715-202223), and indigo (batch number 11016-201612) were purchased from the National Institutes for Food and Drug Control (Beijing, China). Sucrose (batch number TF28230301) was purchased from Jiudian Pharmaceutical (Hunan, China). Dextrin (batch number 20230412B) was purchased from Chemball (https://www.chemball.cn/). Potassium carbonate, potassium acetate, magnesium chloride, potassium nitrate, sodium bromide, potash iodide, ammonium sulfate, soluble starch, and sodium chloride were purchased from Sinopharm Chemical Reagent (https://www.sinoreagent.com/index.jsp). Sodium bromide and ammonium sulfate were purchased from Damao Chemical Reagent Factory (Tianjin, China). Potassium sulfate and potassium chloride were purchased from Xilong Scientific (https://www.xilongs.com/about.html). Acetonitrile of HPLC grade was purchased from Merck (Darmstadt, Germany). High-performance liquid chromatograph (HPLC; LC-20A) was purchased from Shimadzu (Kyoto, Japan). JA5300 Electronic Balance was purchased from Shanghai Balance Instrument Factory (Shanghai, China). KH 5200DB digital ultrasonic cleaner was purchased from Kunshan Ultrasonic Instruments (Kunshan, China).

Extraction Process Research

Preparation of the Extractum

The experimental section was performed according to the traditional water decocting process used in the early clinical stage of the acne granules, combined with the characteristics of medicinal ingredients and extraction conditions. As shown in ►**Table 1**, the formula consists of nine herbal medicines. The total weight was 350 g. The ingredients were mixed evenly according to the formula ratio, soaked in cold water, and decocted, resulting in a concentrated liquid to give a Chinese medicine extract.

Process Optimization

The decocting process was investigated by an orthogonal test. As shown in ►**Table 2**, IBM SPSS statistics software V26 (IBM, New York, United States) was used to design an orthogonal table of four factors and three levels based on a single-factor test. An orthogonal experiment was performed with four factors, namely, the amount of water added, decocting times, extraction time, and soaking time, each having three levels. The optimal extraction process parameters were determined using the extraction yield as a detective marker. The extraction yield was calculated using the following formula: extraction yield $(\%) = (W_1/W_2) \times 100$, where W_1 is the weight of the dried extract and W_2 is the weight of the total herbs.

Preparation of the Acne Granules

The granules were prepared by a wet granulation technology. Briefly, the extractum was mixed with a variety of excipients

Table 1 Plant species and the composition of the Acne Granules

Chinese phonetic alphabet	Botanic family	Botanical nomenclature	Amount (g)
Pi Pa Ye	Rosaceae	Loquat leaves	28.0
Sang Bai Pi	Moraceae	*Santalum Album* L.	28.0
Di Huang	Scrophulariaceae	*Rehmannia glutinosa* Libosch.	94.5
Dan Pi	Ranunculaceae	Tree Peony Bark	28.0
Chi Shao	Ranunculaceae	*Radix Paeoniae Rubra*	28.0
Dan Shen	Lamiaceae	*Radix Salviae*	70.0
Huang Qin	Lamiaceae	*Scutellaria baicalensis* Georgi	28.0
Da Qing Ye	Acanthaceae	Indigowoad Leaf	28.0
Gan Cao Pian	Leguminosae	Raw licorice slices	17.5

Table 2 Factors and levels of the orthogonal experiment

Level	A (times)	B	C (h)	D (h)
1	4	1	1.0	1
2	6	2	1.5	2
3	8	3	2.0	3

Note: A, the amount of water added; B, the decocting times; C, the extraction time; and D, the soaking time.

to make the soft material, sieved to granulate wet particles, and then dried. The indexes affecting the quality of the granules, including the relative density of Chinese medicine extract, the choice of filler, the choice of different mesh screens, and the choice of the ratio of the main drug and auxiliary material, were investigated by a single factor test.

The extractum has a certain viscosity, and appropriate relative density favors the uniform mixing of extractum with the excipients to obtain uniform and beautiful particles. The extractums were prepared according to the optimized decocting process, and the extractums were concentrated via evaporation to achieve a relative density of 1.10 to 1.40 g/mL. Then, the influence of different relative densities of extractum on the preparation of acne particles was investigated.

Sucrose, soluble starch, and dextrin are excipients commonly used in wet granulation. The excipient exhibited high performance, good water solubility, and excellent stability. In this work, the effect of the three excipients on the preparation of acne particles is investigated.

The granules passed the 10 mesh, 14 mesh, and 18 mesh sieve, respectively, and the appropriate mesh number was investigated according to the appearance and particle size characteristics.

Index Evaluation

The reference methods were used to determine the index of acne granules including the particle molding rate, dissolvability, angle of repose, moisture content, and interparticle void ratio,[8,9] as well as the moisture absorption percentage.[10,11]

Molding rate: according to the second method (double screening method) in the particle size inspection method of the 2020 edition of Chinese Pharmacopoeia, the particles that could pass the No. 1 sieve (10-mesh) but could not pass the No. 5 sieve (80-mesh) are qualified. The molding rate is calculated as molding rate = (qualified particle mass/total particle mass) ×100%.

Dissolvability: acne granules were packed in a single dose of 1 bag (12 g), added heated water (200 mL), and stirred for 5 minutes to observe the dissolution of the granules.

The angle of repose: the fixed funnel method was used to calculate the angle of response. Two funnels were placed in series and fixed at a certain distance above a horizontally placed drawing paper. The height of the lower end of the funnel from the paper was H ($H = 2.0$ cm). Qualified particles were added slowly from the upper end of the funnels and allowed to flow naturally. When the tip of the cone formed by the particles comes into contact with the lower end of the funnel, the radius R of the cone formed was recorded, and the angle of repose was calculated as the angle of repose = arctg (H/R).

Moisture content: the moisture content was calculated after the sample was dried to constant weight according to the 2020 edition of Chinese Pharmacopoeia. The initial moisture content = [(initial mass before drying – mass after drying)/initial mass before drying] ×100%.

Interparticle void ratio: the interparticle void ratio was calculated after measuring loose density and vibrating density, and the void ratio = [(vibrating density – loose density)/(loose density × vibrating density)] × 100%.

Moisture absorption percentage: accurately weigh a certain number of particles, set them in a weighing bottle, open the bottle into a dryer filled with a supersaturated solution of sodium chloride, let it stand for 24 hours, and then take out the bottle and weigh it again. Moisture absorption percentage of particles = (wet weight of particles – dry weight of particles)/dry weight of particles ×100%.

Critical Relative Humidity Analysis

Supersaturated solutions of different kinds of salt and water were prepared to investigate the influence of different environmental humidities on the production of granules according to a reported study.[12] Saturated solutions of CH_3COOH, $MgCl_2$, K_2CO_3, NaBr, KI, NaCl, $(NH_4)_2SO_4$, KNO_3, and purified water were placed in a glass dryer with a relative humidity being 22.5, 32.8, 43.2, 57.6, 68.9, 75.3, 81.0, 92.5, and 100.0%, respectively, at a constant temperature of 25°C for 24 hours. The hygroscopicity of the particles (96 hours) under different humidity conditions was measured. The hygroscopicity equilibrium curve was drawn to obtain the critical relative humidity (CRH).

Quality Control of the Acne Granules

Examination Indexes of Granules

Three batches of acne granules were selected for sample verification, and the characteristics, particle size, moisture, load difference, and microbial limit of acne granules were examined according to the 2020 edition of Chinese Pharmacopoeia.

Thin Layer Chromatography Analysis

Three batches of acne granules were selected for the thin-layer chromatography (TLC) analysis of *Radix Salviae*, Indigowoad Leaf, and *Scutellaria baicalensis* according to the thin layer chromatography (General Rule 0502, Part IV, Chinese Pharmacopoeia) test.[8]

Identification of *Radix Salviae*: the solution of the sample, negative control, and controlled medicinal material (5 µL) were spotted manually on the chromatographic plates. A

mixture of toluene:ethyl acetate:formic acid (80:50:8, v:v:v) was used as a developing solvent. It was unfolded, dried, and sprayed with a solution of 2% ferric chloride:1% potassium ferricyanide (1:1, v:v).

Identification of Indigowoad Leaf: the solution of the sample, negative control, and the standard solution of indigotin (10 µL) were dropped on silica gel TLC, then eluted with toluene:acetone (4:1, v:v) as a solvent system.

Identification of *S. baicalensis*: the solution of the sample, negative control, and the standard solution of baicalein (5 µL) were spotted manually on the same silica gel G TLC. Ethyl acetate:butanone:formic acid:water (5:3:1:1, v:v:v:v) was used as an unfolding agent. The samples were visualized with 1% ferric chloride ethanol solution.

Determination of Index Component Content

Quantitative determination of the content was carried out using an LC-20A HPLC (Shimadzu, Kyoto, Japan) system. The separation was performed on an Agilent Eclipse XDB-C18 reversed-phase column (4.6 mm × 250 mm, 5.0 µm). The mobile phase was a mixture of acetonitrile and 0.05% phosphoric acid water (22:78, v/v). The flow rate was 1.0 mL/min. The detection wavelength was 276 nm. The column compartment temperature was maintained at 30°C. The injection volume was 20 µL. All tested solutions were filtered through a 0.2-µm membrane filter before the analysis.

An appropriate amount of baicalin was accurately weighed and added to methanol to prepare a reference solution with a final concentration of 0.15 mg/mL. The solution prepared without baicalin was used as a negative control. The sample solution was prepared by accurately weighing the sample (net quantity: 5 g) in a 50 mL volumetric flask; adding ultrasonic treatment of methanol solution to dissolve it completely, and fixing the volume to the calibration line.

The methodology (linearity ranges, stability, repeatability, precision, and spiked recovery) was investigated according to the Guiding Principles of 2020 Edition of Chinese Pharmacopoeia reviewed and approved by the National Pharmacopoeia Committee.

Three batches of samples (batch numbers: 180414, 180416, and 180423) were taken and configured into a sample solution according to the method mentioned above. 20 µL reference solution and sample solution were precisely taken and injected into the liquid chromatograph to record the chromatogram. The content of baicalin in the sample was calculated from the peak area according to the external standard method.

Results

Experimental Procedure for the Optimization of Extraction Process

As shown in ►**Table 3**, the factors affecting the extraction effect were in the order of (B) > (A) > (C) > (D), i.e., the effect on the experimental results was: the decocting times > amount of water added > extraction time > soaking time in descending order. Range analysis showed that the optimal experimental conditions were $A_2B_3C_1D_2$, i.e., adding six times the amount of water, decocting three times, 1 hour each time, and the initial soaking for 2 hours. Considering the actual production, the hygroscopicity of medicinal materials, energy saving, and time cost, the optimal extraction conditions were modified as follows: nine medicinal materials, the first time adding eight times the amount of water, soaking for 2 hours, and decocting for 1.5 hours. For the second and third time, six times the amount of water, and decocting for 1 hour. Based on these improved conditions, the extract yields were 28.9, 29.4, and 29.8%, respectively, with a relative deviation of 1.54%.

Table 3 Orthogonal experimental design and results

No.	Factors				Extract yield (%)
	A	B	C	D	
1	1	1	1	1	13.4
2	1	2	2	2	19.8
3	1	3	3	3	20.1
4	2	1	2	3	19.3
5	2	2	3	1	24.3
6	2	3	1	2	29.3
7	3	1	3	2	17.8
8	3	2	1	3	25.6
9	3	3	2	1	29.1
K_1	53.30	50.50	68.30	66.80	
K_2	72.90	69.70	68.20	66.90	
K_3	72.50	78.50	62.20	65.00	
R	19.60	28.00	6.10	1.90	
SS	83.66	136.68	8.14	0.76	

Molding Process of the Acne Granules

Extractum Density Screening

As shown in ►**Table 4**, a relative density of 1.30 to 1.40 g/mL of the extracts was preferred for the granulation condition.

Excipient Screening

The excipients including sucrose, soluble starch, and dextrin were assessed according to the indexes of the easy granulation, particle properties, molding rate, etc. As shown in ►**Table 5**, a single excipient resulted in a low molding rate. Then, we mixed the excipients (dextrin:sucrose = 1:3, 1:1, 3:1) to assess the influence of different proportions of the excipients on the preparation of the granules. As shown in ►**Table 6**, the extractum was mixed evenly with the excipients to make soft materials, granulated, and dried. Our data suggested that when the extractum was mixed with a certain proportion of dextrin and sucrose (1:3), the material was soft and suitable; the granulation was easy to pass through the screen; and the particles obtained had good formability and met the requirements. In addition, sucrose, as an excipient, can cover up the bitter taste of TCM and may play the role of a taste modifier, a diluent, and an adhesive in the process.

Mesh Number Screening

The granules passing through the 18-mesh sieve were uniform in appearance and size, and the results were consistent with the particles by an 18-mesh sieve in industrial production, so the screening mesh number of acne granules was selected as 18-mesh.

Ratio of the Main Drug and Excipient Screening

Extractum, sucrose, and dextrin were mixed according to the ratio of the main drug: excipient at 1:3, 1:4, 1:5, and 1:6, respectively. As shown in ►**Table 7**, when the ratio was 1:5, the particle state was the best and the molding rate was the highest.

Process Verification of the Acne Granules

The acne extract was prepared according to the optimal extraction process conditions, 40 g of which with a relative density of 1.30 to 1.40 (20–30°C), 150 g powdered sugar, and

Table 4 Relative density of extractum

No.	Relative density of extractum (g/mL) at 20–30°C	Granulation condition
1	1.10–1.20	The soft material is sticky, easy to stick mesh, and difficult to granulate
2	1.20–1.30	The soft material is sticky, easy to stick mesh, and difficult to granulate
3	1.30–1.40	The soft material is moderate, mixed evenly with auxiliary materials, and easy to granulate

Table 5 Excipient selection

Types	Granulation condition	Granules
Dextrin	The soft material is loose, low viscosity, and uneven, more fine powder	The particle has more white spots and a low molding rate
Sucrose	The soft material is sticky, clumping, easy to stick mesh, and difficult to granulate	Harder particles and a low molding rate
Soluble starch	The soft material is loose, more fine powder	Fragile particles

Table 6 Amount of auxiliary material screening

Dextrin: powdered sugar	Granulation condition	Granules	Moisture content (%)	Angle of repose (°)	Molding rate (%)
1:3	The soft material is uniform, has no obvious clumping, and is easy to granulate	Brown, moderate particle hardness	1.63	29.82	88.95
1:1	The soft material is loose, uneven, white spots	Light brown, harder particles	1.72	30.25	83.28
3:1	The soft material is loose, uneven, and easy to disperse	Light brown, harder particles	3.10	31.80	77.04

Table 7 Ratio screening of the main drug and excipient

Main drug: excipient	Granulation condition	Granules description	Moisture content (%)	Angle of repose (°)	Molding rate (%)
1:3	The soft material is sticky, caking, easy to stick mesh, and difficult to granulate	Brown and harder	/	/	22.52
1:4	Mixed evenly with auxiliary materials, a small amount of lumps in soft material, easy to granulate	Brown, uniform, and harder	2.53	29.82	84.30
1:5	Mixed evenly with auxiliary materials, moderate soft materials, no obvious clumps, easy to granulate	Brown, uniform, and moderate hardness	1.62	27.92	96.09
1:6	The soft material is loose, uneven, noncaking, and easy to granulate, a fine powder is obtained	Light brown and moderate hardness	1.80	28.96	79.48

Table 8 Process verification of the acne granules

Sample batch	Granulation condition	Molding rate (%)	Angle of repose (°)	Particle porosity (%)	Moisture absorption percentage (%)	Dissolvability
Batch 1	Good shape, easy sieving, suitable particle size	96.24	29.68	15.17	5.75	All dissolved within 5 minutes
Batch 2	Good shape, easy sieving, suitable particle size	96.03	29.68	14.96	6.53	All dissolved within 5 minutes
Batch 3	Good shape, easy sieving, suitable particle size	94.30	29.25	15.29	6.00	All dissolved within 5 minutes
RSD (%)	–	1.12	0.84	1.10	5.37	–

Table 9 Result of critical relative humidity

The supersaturated solution	CH_3COOK	$MgCl_2$	K_2CO_3	NaBr	KI	NaCl	$(NH_4)_2SO_4$	KNO_3	H_2O
RH (%) at 25°C	22.5	32.8	43.2	57.6	68.9	75.3	81.0	92.5	100.0
Moisture absorption (%)	0.17	1.70	3.09	3.52	3.95	6.53	20.99	43.48	50.46

Abbreviation: RH, relative humidity.

50 g dextrin were mixed evenly, granulated through an 18-mesh sieve, and dried at 60°C. The granules were passed through a 10-mesh sieve and stored. In this work, three batches of particles were prepared. The quality of soft materials, granulation conditions, fluidity, molding rate, dissolvability, hygroscopicity, and other parameters were assessed to investigate the process; the results are shown in ►**Table 8**.

CRH Determination

The relative humidity (horizontal coordinate) was plotted against the hygroscopic rate (vertical coordinate) to draw the hygroscopic equilibrium curve. The horizontal coordinate corresponding to the intersection of the two tangent lines is CRH, as shown in ►**Table 9** and ►**Fig. 1**. The CRH of acne particles is about 82%, and therefore, the relative humidity of the environment needs to be controlled at 82% or less in acne particles' production and storage to minimize the impact of water on the particles and to ensure its quality.

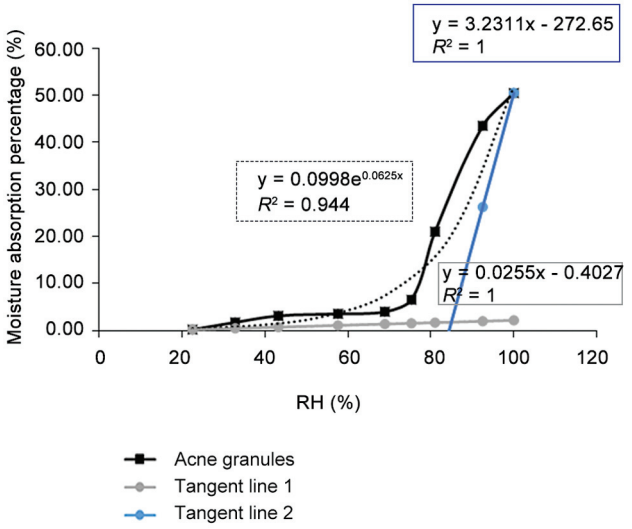

Fig. 1 Moisture absorption curves of acne particles.

Table 10 Examination result of the acne granules

Item	The result of acne granules		
	Batch 1	Batch 2	Batch 3
Granularity	3.8%	4.0%	10.5%
Hydration	1.3%	2.0%	1.8%
Dissolvability	Comply with regulations	Comply with regulations	Comply with regulations
Load variance	Comply with regulations	Comply with regulations	Comply with regulations
Microbial limit	Meet the specification	Meet the specification	Meet the specification

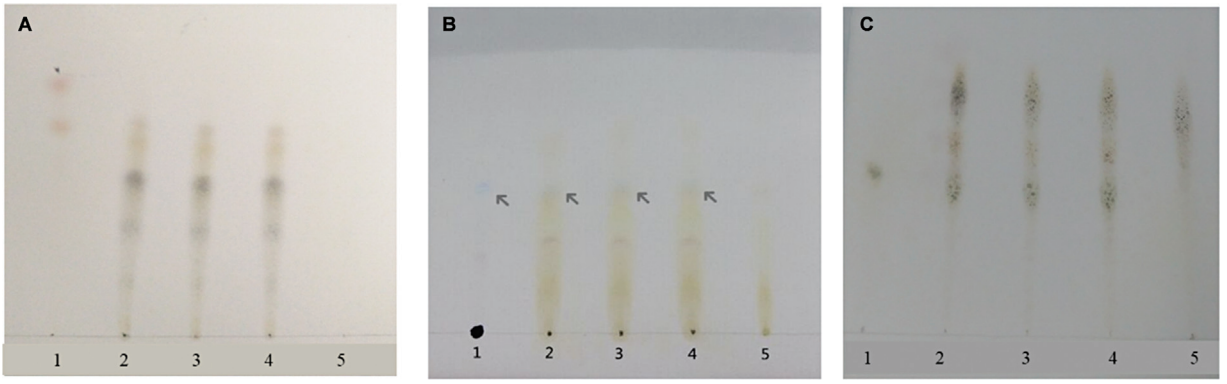

Fig. 2 TLC of (**A**) *Radix Salviae*, (**B**) Indigowoad Leaf, and (**C**) *Scutellaria baicalensis* in acne granules; 1: reference drugs, 2–4: test samples, 5: negative control. TLC, thin-layer chromatography.

Quality Control of the Acne Granules

The Indexes of the Acne Granules

Acne granules are brown to tan granules with a sweet, slightly bitter taste. The parameters determined are listed in ►**Table 10**, which are in line with Pharmacopeia standards.

TLC Analysis

As shown in ►**Fig. 2**, the TLC chromatogram of the three batches of samples showed the same color spots at the corresponding positions of the chromatogram of the control medicinal materials while no spots at the corresponding positions of the negative control, suggesting no interference. Given the above, the method of thin-layer identification of *Salviae*, Indigowoad Leaf, and *S. baicalensis* was stable.

Method Validation for Quantitative Determination

HPLC was used to determine the content of baicalin in acne granules. As shown in ►**Fig. 3**, the chromatographic peak was well separated and the other components did not

Table 11 Test results of recovery rate ($n = 3$)

Sample amount (g)	Peak area	Total measured amount (μg)	Known content (μg)	Added amount (μg)	Recovery rate (%)	Average recovery (%)	RSD (%)
5.0007	16,102,384	2,112.97	1,079.32	1,040	99.39	99.96	1.50
5.0012	16,806,972	2,202.43	1,145.24	1,040	101.66		
5.0002	16,021,757	2,102.74	1,074.91	1,040	98.83		
5.0003	17,786,245	2,326.77	1,033.43	1,300	99.49	99.53	0.17
5.0004	18,003,945	2,354.41	1,058.13	1,300	99.72		
5.0010	18,560,849	2,425.12	1,133.24	1,300	99.38		
5.0015	20,895,105	2,721.50	1,162.07	1,560	99.96	99.53	0.48
5.0005	20,066,841	2,616.33	1,062.31	1,560	99.62		
5.0007	20,475,707	2,668.25	1,123.54	1,560	99.02		

Abbreviation: RSD, relative standard deviation.
Note: Take nine shares of the powder of acne granules with a given content, each share 5.0 g. Weigh them precisely and then add the suitable amount of the reference substance solution precisely. According to the way of preparing the sample solution, we make three shares of the test solutions with three different concentrations.

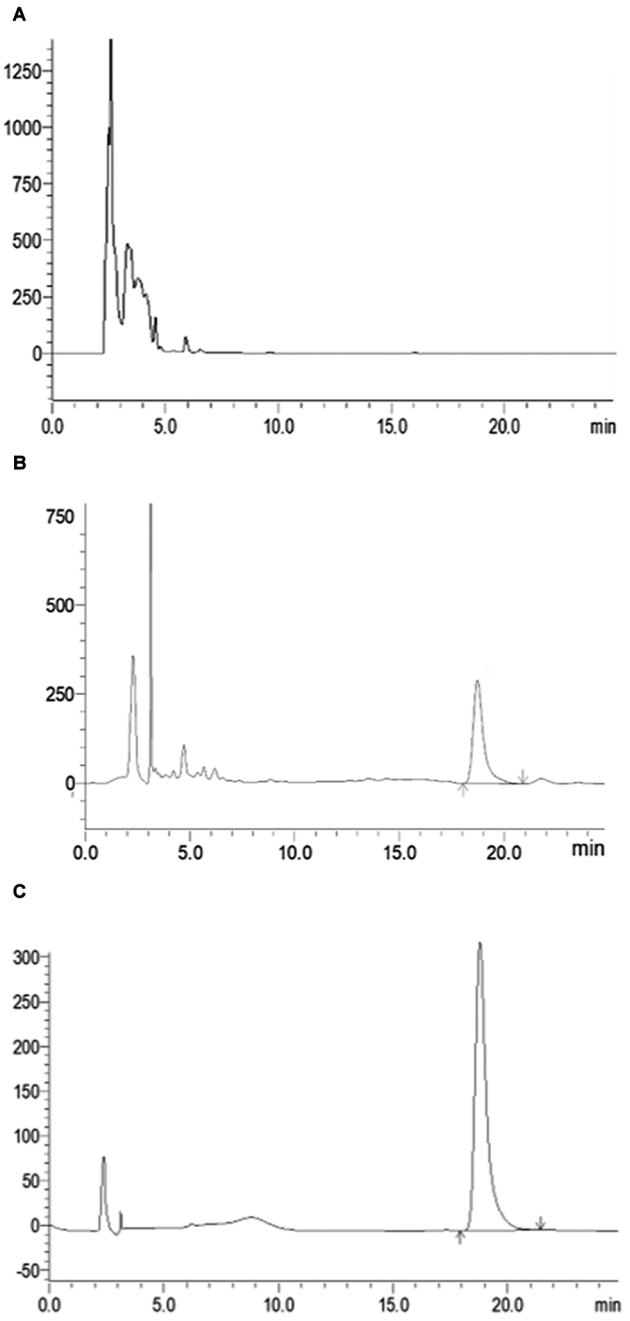

Fig. 3 HPLC chromatograms. (**A**) Negative control. (**B**) Sample solution. (**C**) Reference substance solution. HPLC, high-performance liquid chromatography.

interfere with the determination. The number of theoretical plates was more than 2,000. The results suggested that the method has good system suitability. The retention time of baicalin was 17 minutes, and the regression equations of baicalin were $y = 78760x - 539391$ ($R = 0.9996$), in the experimental range of 50 to 250 µg/mL, indicating a good linear relationship within the determination range and a good sensitivity under the chromatographic conditions developed.

The relative standard deviation (RSD) of peak areas' precision of baicalin was 1.72%, indicating that the established method had high precision. The RSD of peak areas' stability was 0.57%, indicating that the test solution was stable within 24 hours. The RSD of the reproducibility test was 1.22%, indicating that the method had good reproducibility. The mean recoveries ranged from 99.53 to 99.96% with RSDs of 0.17 to 1.50%, as shown in ►**Table 11**. The above results indicated the high accuracy of the analytical method.

Content Determination

Three batches of acne granules were selected for content determination. As shown in ►**Table 12**, the average content of baicalin in each bag (1 g) of granules was 1.16, 1.78, and 1.35 mg, respectively. Considering the origin of the raw materials, the harvesting season, and the batch of the granules, it was determined that the content of baicalin in acne granules was not less than 1.0 mg per bag (1 g).

Discussion

The process of preparing TCM compound preparations generally includes pretreatment, extraction, separation and refinement, concentration, drying, molding, etc. In the production process, each production and processing link has an important impact on the quality, efficacy, and safety of TCM preparations. In this work, the traditional water extraction technology was used to prepare acne granules. The optimal decoction process was assessed by optimizing the extraction method through an orthogonal experiment and using the extraction rate of the extract as a comprehensive evaluation index.[13]

Excipients have an important effect on granulation difficulty and granule quality. Our data showed that the mixing of powdered sugar and dextrin with the main drug (5:1) resulted in a particle molding rate of up to 96.09%, which was superior to the mixing of powdered sugar and dextrin alone with the main drug. We further confirmed the optimal composition of the prescription and the process parameters for the preparation of acne particles. With the optimal process in hand, the granules obtained met the requirements of granules in the 2020 edition of Chinese Pharmacopoeia.

The acne granules are derived from ancient classical formulas with a complex herbal composition. In this work, we used a TLC method to confirm the presence of *S. baicalensis*, *Radix* green leaf, and *Salvia miltiorrhiza*, respectively. Baicalin is the main active ingredient of *S. baicalensis*, the royal medicine in the formulation, which has the effects of clearing heat and dampness, purging fire and detoxifying, stopping bleeding, and calming fetus.[14] *Scutellaria baicalensis* has antioxidant, antibacterial, and immunomodulatory effects.[15,16] *Scutellaria baicalensis* and its active components inhibit the growth of bacteria, fungi, and chlamydia, which may be related to the inhibition of ATP synthase, the formation of microbial membranes, and the expression of certain proteins.[17] *Scutellaria baicalensis* also has an obvious antibacterial effect on *Staphylococcus aureus* and other pathogenic bacteria,[18,19] In addition, baicalin has a certain anti-inflammatory effect, and can effectively inhibit

Table 12 Quantification of baicalin in acne granules ($n = 3$)

Sample batch	Sample	Peak area	Concentration (μg/mL)	Content (μg/g)	Average content (mg/g)
180414	1-1	7,965,466	107.77	1,077.70	1.16
	1-2	8,549,045	115.67	1,156.66	
	2-1	8,759,041	118.51	1,185.07	
	2-2	9,119,286	123.38	1,233.81	
180416	1-1	12,908,098	174.64	1,746.42	1.78
	1-2	12,954,786	175.27	1,752.74	
	2-1	13,103,177	177.28	1,772.82	
	2-2	13,685,744	185.16	1,851.63	
180423	1-1	10,153,732	137.38	1,373.77	1.35
	1-2	9,768,167	132.16	1,321.60	
	2-1	9,971,863	134.92	1,349.16	
	2-2	10,047,317	135.94	1,359.37	

inflammatory response.[20,21] Therefore, an HPLC method based on the content of baicalin was established in the study. The method was simple, stable, and accurate, and the content of baicalin determined can be used as the quality control index of the acne granule preparation.

Antibiotics are widely used to treat acne at home and abroad; however, their long-term use is prone to toxicity and side effects such as double infection and drug resistance.[22] The acne granules is a TCM compound preparation, which can effectively avoid the drawbacks of antibiotics, and has stable clinical application in acne therapy. Meanwhile, granule preparation has obvious advantages in dosage, storage, transportation, quality detection, and other aspects, and is suitable for popularization. Considering that the clinical use of a drug is treatment-oriented, and to enhance the therapy efficacy, it is recommended to use anti-infection and cuticle-stripping agents to reduce inflammation in the administration.

Conclusion

In this study, an orthogonal experiment was used to optimize the extraction process of acne granules. The extraction process was set as follows: soaked for 2 hours, boiled three times, decocted with eight times the amount of water for 1.5 hours for the first time, and six times the amount of water for 1 hour for the second and third times. At the same time, the preparation process of acne granules was optimized, and the ratio of extract to excipient was 1:5. Dextrin to powdered sugar was 1:3. The optimized process has a positive significance for improving production efficiency and reducing production costs. The quality of acne granules prepared using the above process was further analyzed. The results showed that acne granules had good dissolution effect, stability, uniform particle size, suitable moisture content, and good repeatability and recovery. TLC identification of representative medicinal materials showed that the quality of the preparation was stable and controllable. In summary, the preparation process is reasonable and feasible, the quality is stable, the quality control method is simple, and it is suitable for industrial mass production.

Conflict of Interest
None declared.

Acknowledgment
We thank Dr. Ruikang Cai, Director of Dermatology, Air Force Medical Center, for the empirical prescription.

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