Optimization of the Formulation Process for Zhuang Medicine Yishanhong Granules by Orthogonal Design

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Abstract [**Objectives**] To screen the optimal formulation process for Zhuang Medicine Yishanhong Granules. [**Methods**] An $L_9(3^4)$ orthogonal design was employed to optimize the granulation process, with comprehensive assessment based on the granule yield, moisture absorption, flowability, and color uniformity. The factors investigated included the amount and ratio of excipients, and the mesh size of the sieve. [**Results**] The optimized parameters were as follows: a 3∶2 ratio of dextrin to mannitol as excipients, a 1∶3 ratio of extract to excipients, and a 14-mesh sieve. Under these conditions, Zhuang Medicine Yishanhong Granules were successfully obtained. [**Conclusions**] The optimal formulation process for Zhuang Medicine Yishanhong Granules was determined. The granules prepared under these conditions exhibited a satisfactory formation rate, along with favorable properties in terms of moisture absorption, flowability, dispersibility, and color uniformity. This process is rational and feasible, thereby providing a reliable basis for industrial production.

Key words Zhuang Medicine Yishanhong Granules, Orthogonal test, Formulation process

1 Introduction

Zhuang Medicine Yishanhong is a traditional Zhuang formula from Guangxi Zhuang Autonomous Region, mainly used to combat hepatitis B. Composed of five medicinal materials, including *Viburnum fordiae* Hance and *Hypericum japonicum* Thunb., it is known to eliminate pathogens and toxins, clear damp-heat and resolve stasis, dredge the 'liver road' (biliary tract), and reinforce healthy qi. It demonstrates protective effects against liver injury induced by hepatitis B and can enhance immune function. Its primary active constituents are flavonoids and phenolic acids[1-2], and it also contains volatile components[3].

Studies have demonstrated that both the water and alcohol extracts of Zhuang Medicine Yishanhong exhibit protective effects against CCl_4-induced acute liver injury[4]. Besides, they significantly ameliorate CCl_4-induced liver fibrosis in rats. The underlying mechanism is potentially associated with the regulation of signaling pathways involved in DNA replication and tryptophan metabolism[5]. Zhuang Medicine Yishanhong Granules exert hepatoprotective, spleen-fortifying, and cholagogic effects in an ANIT-induced cholestatic rat model. The mechanism is achieved by modulating the Farnesoid X receptor (FXR) and the expression of bile acid transporters regulated by it[6]. An efficacy screening conducted in HepG2.2.15 cells demonstrated that both the water and alcohol extracts of Zhuang Medicine Yishanhong, at various concentrations, exhibited inhibitory effects on the secretion of HBsAg and HBeAg[7]. Zhuang Medicine Yishanhong Granules are produced by further extracting, purifying, and concentrating the traditional decoction, followed by the addition of excipients. This process not only preserves the therapeutic advantages of the traditional decoction but also reduces the required dosage. Our research team has demonstrated that the optimized extraction process is stable and feasible, yielding a high extraction rate of active constituents. This method is suitable for industrial-scale production, thereby providing a reliable basis for the formulation research and manufacturing of the granules[8-9]. Based on preliminary and single-factor tests, this study employed an orthogonal design to optimize the critical factors affecting granulation. The optimization was guided by a comprehensive assessment of granule yield, moisture absorption, flowability, and color uniformity, leading to the identification of the optimal formulation process for Zhuang Medicine Yishanhong Granules.

2 Materials and methods

2.1 Instruments BS224S electronic balance (Sartorius Systems Instrument Co., Ltd., Beijing); YP50001 electronic balance (Yuyao Jinnuo Balance Instrument Co., Ltd.); HH-S4 digital constant temperature water bath (Jintan Medical Instrument Factory); GZX-9420MBE electric thermostatic blast drying oven (Shanghai Boxun Industrial Co., Ltd. Medical Equipment Factory).

2.2 Reagents Soluble starch (Anhui Shanhe Pharmaceutical Excipients Co., Ltd., No.: 150302); Dextrin (Liaoning Dongyuan Pharmaceutical Co., Ltd., No.: 20150073); Microcrystalline cellulose (Shandong Guangda Technology Development Co., Ltd., No.: 20150208); Mannitol (Guangxi Nanning Chemical Pharmaceutical Co., Ltd., No.: F869B).

2.3 Medicinal materials Rhododendri Daurici Folium refers to the dried rhizome of *Viburnum fordiae* Hance (Zhuang name: *Go'gyangngoenz*) from the Caprifoliaceae family; *Hypericum japonicum* refers to the dried whole plant of *Hypericum japonicum*

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Thunb. (Zhuang name: *Rumdenzgihvangz*) from the Clusiaceae family; Huanggen is the root of *Prismatomeris connata* Y. Z. Ruan (Zhuang name: *Raghenj*) from the Rubiaceae family; Maojigucao is the entire plant of *Abrus mollis* Hance (Zhuang name: *Rumndokgaeq*) from the Fabaceae family; Niudali is the rhizome of *Millettia speciosa* Champ (Zhuang name: *Gorengxmox*) from the Fabaceae family. All Zhuang Medicine Yishanhong medicinal materials were purchased from the Guangxi Yulin Medicinal Market and authenticated by Professor Wei Songji from the College of Zhuang Medicine at Guangxi University of Chinese Medicine.

2.4 Preparation of extract The optimal extraction process for Zhuang Medicine Yishanhong Granules has been previously determined as follows[9]: we weighed the medicinal materials according to the prescription, added 12 times the amount of water for the first extraction, and soaked for 60 min. For the second and third extractions, added 10 times the amount of water each time and decocted for 60 min per cycle, for a total of three extractions. Then, we combined the filtrates, concentrated to a solid-to-liquid ratio of 1∶1, added ethanol until the alcohol content reached 50%, and let it stand for 48 h. After filtration, concentrated the solution to an extract with a relative density of approximately 1.36 (at 25 ℃). Stored the extract at 4 ℃ for later use.

2.5 Orthogonal test design[10] Based on single-factor experiments and preliminary trials, the main factors affecting the formation process were screened. The ratio of diluents (dextrin∶mannitol), the amount of excipients (excipients∶extract), and the mesh size of the sieve were selected as investigation factors. The evaluation indicators included formation rate, moisture absorption rate, color uniformity of the granules, flowability, and solubility. The optimal formation process conditions for Zhuang Medicine Yishanhong Granules were determined using an $L_9(3^4)$ orthogonal design, with the factor levels presented in Table 1.

Table 1 Factor level of Zhuang Medicine Yishanhong Granules molding process optimized by orthogonal design method

Level	Factor		
	Dextrin∶mannitol (A)	Excipients∶extract (B)	Granulation mesh (C)
1	2∶2	2.5∶1	10
2	3∶2	3.0∶1	14
3	4∶2	3.5∶1	20

2.6 Determination of granule inspection indicators

2.6.1 Qualified granule rate. According to the provisions of Item 0982 in the *General Rules for Preparations of the Chinese Pharmacopoeia* (2020 Edition)[11], granules that pass through a No. 1 sieve but cannot pass through a No. 5 sieve are defined as qualified granules. The yield of qualified granules is calculated as: (Weight of qualified granules/Total weight of granules) × 100%.

2.6.2 Moisture absorption rate. Took 1 g of granules prepared with different excipients, placed them in a flat weighing bottle that has been dried to constant weight, and weigh accurately. Opened the lid and place the bottle in a desiccator containing a saturated NaCl solution at the bottom. Maintained the setup at 25 ℃, where the relative humidity inside the desiccator was 75%. After 48 h, quickly and accurately weighed the bottle. Calculated the moisture absorption rate using the formula: Moisture absorption rate (%) = [(Weight after absorption − Weight before absorption)/Weight before absorption] × 100%.

2.6.3 Color uniformity. Scoring criteria: This item has a maximum score of 10 points. Granules that are uneven with inconsistent color score 0 − 2.5 points; granules with generally uniform color score 2.6 − 5.0 points; granules with relatively uniform color score 5.1 − 7.5 points; granules that are uniform and consistent in color score 7.6 − 10 points.

2.6.4 Flowability[12-13]. The angle of repose of the granules was determined using the fixed funnel method. Three funnels were connected in series and fixed at a height (h) above horizontally placed graph paper. The granules were slowly and uniformly poured along the wall of the top funnel until the tip of the resulting granules cone just reached the orifice of the bottom funnel. The diameter (R) of the granules cone was directly read from the graph paper. The angle of repose was calculated using the formula $\tan\alpha = 2h/R$. The measurement was repeated three times, and the average value was taken.

2.6.5 Solubility. Took 10 g of the granules, added 200 mL of heated water, and stirred for 5 min. Observed immediately. The granules should completely dissolve or show slight turbidity.

2.6.6 Critical Relative Humidity (CRH) of the granules. Saturated salt solutions of different concentrations were prepared in separate glass desiccators and allowed to stand at room temperature for 24 h to achieve internal equilibrium. Seven 1 g samples of Zhuang Medicine Yishanhong Granules were weighed, each spread evenly in a flat weighing bottle previously dried to constant weight, forming a layer approximately 2 mm thick. The bottles were accurately weighed, their lids were opened, and they were placed in desiccators containing the different saturated salt solutions. These desiccators were stored in a constant temperature incubator at 25 ℃ for 48 h. Afterwards, the weighing bottles were removed, their lids were closed immediately, and they were accurately weighed again. The moisture absorption percentage was calculated for each sample. A graph was plotted with the relative humidity (RH) as the abscissa (X-axis) and the moisture absorption percentage of the granules as the ordinate (Y-axis). Tangents were drawn to the two ends of the resulting curve, and the abscissa value (RH) corresponding to the intersection point of these two tangents was identified as the CRH of the granules.

2.7 Granule preparation An appropriate amount of the extract was taken, and experiments were conducted according to the formulations and processes outlined in the orthogonal array. Excipients were added to the extract and mixed uniformly. Subsequently, 85% ethanol was sprayed into the mixture to prepare a moist

mass. This mass was then sieved, dried at 60 ℃ for 40 min, and finally sized to obtain the granules.

3 Results and analysis

3.1 Orthogonal test results As shown in Tables 2 and 3, the order of significance of the factors affecting the evaluation indicators was B > A > C, with factors A and B showing statistically significant differences ($P < 0.05$). After comprehensive consideration, the optimal process conditions were determined as $A_2B_2C_2$, specifically: a dextrin-to-mannitol ratio of 3 ∶ 2, an excipient multiple of 3, and sieving through a 14-mesh sieve.

Table 2 Test results of Zhuang Medicine Yishanhong Granules molding process optimization by orthogonal design method

Test	Factor				Qualified	Moisture	Color	Comprehensive
No.	A	B	C	D	granule rate//%	absorption rate//%	uniformity//points	score//points
1	1	1	1	1	83.73	7.34	5	88.42
2	1	2	2	2	89.20	7.71	6	92.95
3	1	3	3	3	82.57	7.87	5	87.50
4	2	1	2	3	85.59	8.15	9	93.42
5	2	2	3	1	90.31	8.16	9	96.56
6	2	3	1	2	81.84	8.67	8	89.77
7	3	1	3	2	80.83	9.44	7	87.87
8	3	2	1	3	87.25	9.12	7	92.23
9	3	3	2	1	80.65	8.79	6	86.94
K_1	89.623	89.903	90.140	90.640				
K_2	93.250	93.913	91.103	90.197				
K_3	89.013	88.070	90.643	91.050				
R	4.237	5.843	0.963	0.853				

Table 3 Orthogonal analysis of variance

Factor	Sum of squared deviations	Degree of freedom	F ratio	F critical value	Significance
A	31.474	2	28.796	19.000	$P < 0.05$
B	53.586	2	49.027	19.000	$P < 0.05$
C	1.393	2	1.274	19.000	$P > 0.05$
Error	1.09	2			

NOTE $F_{0.05}(2,2) = 19.000$.

It is generally accepted that an angle of repose < 40° can meet the flowability requirements during the production process. As shown in Table 4, the granules exhibited good flowability in the tests, and their solubility also generally met the requirements.

Table 4 Determination of orthogonal test angle of repose and solubility

Test No.	Angle of repose	Solubility
1	31.8°	Dissolved completely, with slight turbidity
2	33.5°	Dissolved completely, with slight turbidity
3	35.3°	Dissolved completely, with slight turbidity
4	33.3°	Dissolved completely, with slight turbidity
5	34.0°	Dissolved completely, with slight turbidity
6	32.5°	Dissolved completely, with slight turbidity
7	32.3°	Dissolved completely, with slight turbidity
8	32.8°	Dissolved completely, with slight turbidity
9	33.5°	Dissolved completely, with slight turbidity

3.2 Verification test The verification test was conducted according to the selected optimal formulation conditions: 3 times the amount of excipients (dextrin ∶ mannitol = 3 ∶ 2) and 0.2% aspartame were added, mixed uniformly, and moistened with an appropriate amount of 85% ethanol (approximately 25%) to form a moist mass. The mass was thoroughly blended, sieved through a 14-mesh screen for granulation, dried at 60 ℃ for approximately 40 min, and then sized through a 14-mesh screen to obtain Zhuang Medicine Yishanhong Granules. The qualified granule rate, moisture absorption rate, and flowability of three resulting batches were determined, and color uniformity was scored. The results are shown in Table 5.

Table 5 Verification test results

Test No.	Qualified granule rate//%	*RSD* %	Moisture absorption rate//%	*RSD* %	Color uniformity score//points
1	90.17	1.91	8.32	0.71	9
2	92.09		8.18		8
3	87.88		8.23		8

As shown in Table 5, the granules obtained from the verification test exhibited good formability with minimal fine powder, uniform color, and a high comprehensive score. These results indicate that the final formulation process for Zhuang Medicine Yishanhong Granules is feasible and stable, thereby demonstrating the reliability of the orthogonal experimental results.

3.3 Granule flowability The angle of repose of Zhuang Medicine Yishanhong Granules prepared using the optimal process was 30.77°($n = 3$), indicating good flowability of the granules.

3.4 Granule CRH It can be seen from Table 6 and Fig. 1 that the CRH of the Zhuang Medicine Yishanhong Granules is about 65%. During the production and packaging of the preparation, the relative humidity of the environment should be controlled below 65% to ensure the moisture absorption stability of the particles. However, GMP requires that the relative humidity of the actual production workshop is 45% – 65%, so the Zhuang Medicine Yishanhong Granules meets the requirements of actual production and mass production.

Table 6 Determination of granule CRH (25 ℃) %

NaOH solution	RH at 25 ℃	Moisture absorption rate
37.45	25	2.58
33.28	35	3.55
29.86	45	4.84
26.42	55	6.23
22.80	65	8.58
18.80	75	11.61
13.32	85	16.92

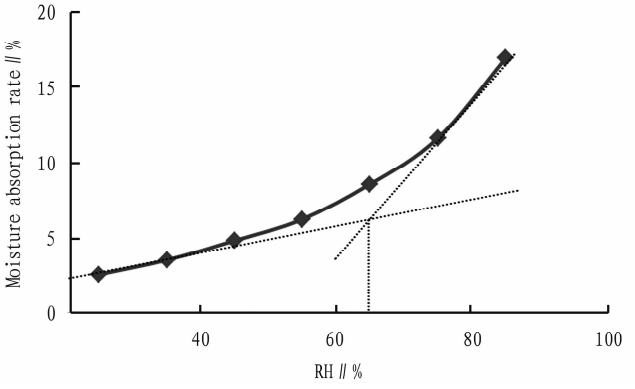

Fig. 1 Moisture absorption curve of Zhuang Medicine Yishanhong Granules

4 Discussion

In this study, we identified the selection of appropriate excipients and their ratios as one of the critical factors influencing the formation process of Zhuang Medicine Yishanhong Granules. The choice of excipients considered not only the product quality and safety but also the cost and suitability for large-scale production. Dextrin serves as a commonly used pharmaceutical excipient with stable properties and low cost. Mannitol is non-hygroscopic, readily soluble in water, chemically stable, and inert towards most active components. Preliminary and single-factor tests revealed that using a blend of dextrin and mannitol as composite excipients yielded superior results compared to single excipients or alternatives like soluble starch and microcrystalline cellulose. This combination produced granules that were firm, well-rounded, with excellent formability and low hygroscopicity. Therefore, we selected a mixture of dextrin and mannitol as the final excipient system, with optimal ratios determined as follows: extract relative density of approximately 1.36 (25 ℃), dextrin-to-mannitol ratio of 3 ∶ 2, and excipient-to-extract ratio of 3 ∶ 1.

The extract of Zhuang Medicine Yishanhong is highly viscous and carries a bitter and acrid taste. Although mannitol in the excipients provides some masking effect, it still cannot fully counteract the undesirable flavor. Therefore, a small amount of aspartame was added as a flavoring agent to improve patient compliance. Aspartame is considered safe and reliable, with an acceptable daily intake range of 0 – 40 mg/kg for adults. It is low in calories or calorie-free and does not affect the metabolism of patients with diabetes or obesity[14]. In this study, the aspartame dosage used was 0.2%, which is far below the safe daily intake limit.

The original formulation of Zhuang Medicine Yishanhong was a water-based decoction. Guided by Zhuang medical theory, we applied modern pharmaceutical preparation technology and optimized the formulation process of Zhuang medicine Yishanhong Granules using an orthogonal experimental design. Process validation was subsequently conducted. The resulting granules exhibited a brownish-yellow color, a faint odor, and slight bitterness. Comprehensive evaluation demonstrated favorable characteristics in terms of formability, hygroscopicity, flowability, uniformity, and solubility, meeting the requirements for industrial-scale production. This study provides a foundation for the large-scale manufacturing of Zhuang Medicine Yishanhong Granules and promotes the development of modern preparations in Zhuang medicine.

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by increasing Ca^{2+} influx. This mechanism likely contributes positively to maintaining intestinal motility and overall gastrointestinal physiological function.

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