Research on the Preparation Process of Mahuang Xixin Fuzi Decoction Granules

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Abstract

Objective The objective of this study was to investigate the preparation process of Mahuang Xixin Fuzi decoction granules based on the clinical pharmacological effects of the classic formulas and to control the quality of the product.

Methods An orthogonal experimental design was used, with extraction yield and transfer rate of key ingredients as evaluation indicators, to optimize the extraction process of Mahuang Xixin Fuzi decoction. The granulation process was optimized based on indicators such as granule formation rate, dissolution rate, and moisture absorption rate.

Results The optimal extraction process for Mahuang Xixin Fuzi decoction was determined as the following: using 10 times the amount of water to soak for 30 minutes, extracting three times, each for 60 minutes, with a concentrated extract relative density of 1.3 g/mL. A mixture of dextrin and starch at a 1:2 ratio was used as a binder for wet granulation. The granule formation rate, dissolution time, and dilution rate of three repeated batches showed relative standard deviation (RSD) values of 1.48, 2.83, and 1.55%.

Conclusion This method is stable and feasible, providing valuable data for the industrial production of Mahuang Xixin Fuzi decoction granules and further research on this formulation.

Keywords
- Mahuang Xixin Fuzi decoction
- granules
- preparation process
- Zhang Zhongjing
- *Treatise on Cold Damage (Shang Han Lun)*

Introduction

Mahuang Xixin Fuzi decoction is a famous formula from Zhongjing Zhang's *Treatise on Cold Damage (Shang Han Lun)* in the Han dynasty, which states: "In the case of Shaoyin disease, if the patient initially presents with fever and a deep pulse, this formula should be used." This formula is included in the *Catalog of Ancient Classic Formulas (Second Batch)* in China.[1] As a representative formula for treating yang deficiency and external pathogenic invasion, Mahuang Xixin Fuzi decoction addresses the deficiency of yang and the body's weakness to expel pathogens. It works internally by stimulating kidney yang and strengthening healthy qi, and externally by expelling cold pathogens and promoting the function of the defensive qi. Clinically, it is often used to treat allergic rhinitis,[2–4] asthma,[5,6] congenital myasthenia syndrome,[7] and sick sinus syndrome.[8–11] Currently, there is limited research on the various dosage forms of Mahuang Xixin Fuzi decoction. Based on the traditional usage characteristics of this formula, this study focuses on preparing it into granules and investigating the extraction process of the decoction, using key active ingredients such as ephedrine hydrochloride, pseudoephedrine hydrochloride, and asarinin as the evaluation indicators for the concentration process. Three critical factors for granule preparation—granule

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formation, moisture absorption, and dissolution—are considered, and a detailed analysis of the density of the extract, types, and ratios of excipients, and the mixing ratio of excipients with the extract was performed to identify the optimal granulation process.

Materials

Drugs and Reagents

Mahuang (Ephedrae Herba), Xixin (Asari Radix et Rhizoma) and Heishunpian (Henan Huaxia Medicinal Materials Co., Ltd., China, Batch No.: 240201, 230501, and 230803) were inspected according to the relevant provisions in Part 1 of the 2020 edition of the *Chinese Pharmacopoeia*. The results show that the Mahuang (Ephedrae Herba) contains 0.797% ephedrine hydrochloride and 0.922% pseudoephedrine hydrochloride. The limit check for the alkaloid ester content in Fuzi (Aconm Lateralis Radix Praeparaia) was 0.0043%. No Aristolochic acid I was detected in Xixin (Asari Radix et Rhizoma), and its volatile oil content was 2.30%, with an asarinin content of 0.230%. All of the above tests comply with the standards of the *Pharmacopoeia*. Ephedrine hydrochloride (purity: 99.9%), pseudoephedrine hydrochloride (purity: 99.9%), and asarone (purity: 99.9%) were purchased from the National Institutes for Food and Drug Control in China (Batch No.: 171241-202310, 171237-202211, 111889-202106). Acetonitrile and methanol (analytically pure reagent, Thermo Fisher Scientific Inc., USA, Batch No: F22MCG201, F22MAJ201).

Instruments

The instruments used were 1260 Series High-Performance Liquid Chromatograph (Agilent Technologies Inc., USA); FA2004 electronic balance with a precision of 0.0001 g (Shanghai Sunny Hengping Scientific Instrument Co., Ltd., China); ME55 electronic balance with a precision of 0.00001 g [Mettler Toledo, Switzerland]; SHB-II circulating water multipurpose vacuum pump [Zhengzhou Great Wall Science & Technology Co., Ltd., China]; KQ-300V ultrasonic cleaner [Kunshan Ultrasonic Instrument Co., Ltd., China]; Best-R laboratory-grade water purifier [Zhiang Instruments (Shanghai) Co., Ltd., China]; HH-1 electric constant-temperature water bath (Beijing Yongguangming Medical Instruments Co., Ltd., China); 101-3 electric hot air drying oven (Beijing Kewei Yongxing Instrument Co., Ltd., China); Pharmacopoeia Sieve No. 1 and No. 5 (Shangyu City Wusi Instrument Sieve Factory, China), etc.

Methods and Results

Drug Dosage Verification

According to the records in *Treatise on Cold Damage* (*Shang Han Lun*) and the *Catalog of Ancient Classic Formulas* (*Second Batch*), the formula for Mahuang Xixin Fuzi decoction consists of two liang of Mahuang (Ephedrae Herba; with stems removed), two liang of Xixin (Asari Radix et Rhizoma), and one piece of Fuzi (Aconm Lateralis Radix Praeparaia; processed, skin removed, broken into 8 pieces). Preparation and usage: First, boil Mahuang (Ephedrae Herba) with 1 dou (~2,000 mL) of water, reduce by 2 sheng (~400 mL), remove the scum, then add the other ingredients; boil until 3 sheng (600 mL) remain, remove the residue, and take 1 sheng (200 mL) warm, three times daily. Based on the reference literature,[12] 1 liang is approximately 15.4 g or 15.625 g, which can be rounded to 15 g, 1 dou = 2,000 mL, and 1 sheng = 200 mL. Therefore, the dosage of Mahuang (Ephedrae Herba) and Xixin (Asari Radix et Rhizoma) is 30 g each. According to studies on "one piece of Fuzi (Aconm Lateralis Radix Praeparaia)" in classical prescriptions,[13,14] clinical dosage habits, guidelines on dosage and usage from the *Pharmacopoeia*, and the current types of processed Fuzi (Aconm Lateralis Radix Praeparaia) used, it is decided to use Heishunpian for Aconite, with one piece of Fuzi (Aconm Lateralis Radix Praeparaia) weighing approximately 15 g. Hence, the formula used in this study consists of 30g of Mahuang (Ephedrae Herba), 30 g of Xixin (Asari Radix et Rhizoma), and 15 g of Fuzi (Aconm Lateralis Radix Praeparaia).

Extraction Process Optimization

Preparation of the Standard Solution

Take 30 g of Mahuang (Ephedrae Herba), add 2,000 mL of water, and bring it to a boil. Then reduce the heat and continue simmering until the remaining liquid is approximately 1,600 mL (about 30 min). Add 15 g of Fuzi (Aconm Lateralis Radix Praeparaia) and 30 g of Xixin (Asari Radix et Rhizoma) and continue simmering until the remaining liquid is approximately 600 mL (about 1.5 h). Filter the mixture through gauze, then concentrate the liquid to about 250 mL to obtain the standard decoction solution of Mahuang Fuzi Xixin decoction.

Preparation of the Test Solution

Take 10 mL of the standard decoction solution obtained in the section "Preparation of the Standard Solution," concentrate it, dissolve in methanol, and dilute to a volume of 10 mL. Filter through a microporous membrane (0.45 μm). The filtrate is the test solution.

Preparation of the Control Solution

Weigh appropriate amounts of ephedrine hydrochloride, pseudoephedrine hydrochloride, and asarone control substances accurately, and place them in the same volumetric flask. Dissolve in methanol, dilute to the mark, and prepare a mixed control solution with concentrations of 0.0426 g/L, 0.1024 g/L, and 0.0410 g/L for ephedrine hydrochloride, pseudoephedrine hydrochloride, and asarone, respectively.

Chromatographic Conditions

Venusil XBP C_{18} column (4.6 × 250 mm, 5 μm); mobile phase: acetonitrile (A)—0.1% phosphoric acid aqueous solution (B); gradient elution program: 0 to 23rd min (5%A), 23rd to 31st min (20%A), 31st to 38th min (25%A), 38th to 43rd min (30%A), and 43rd to 71st min (50%A); detection wavelengths (dual channels): 210 nm and 287 nm; column temperature: 26°C; injection volume: 5 μL.

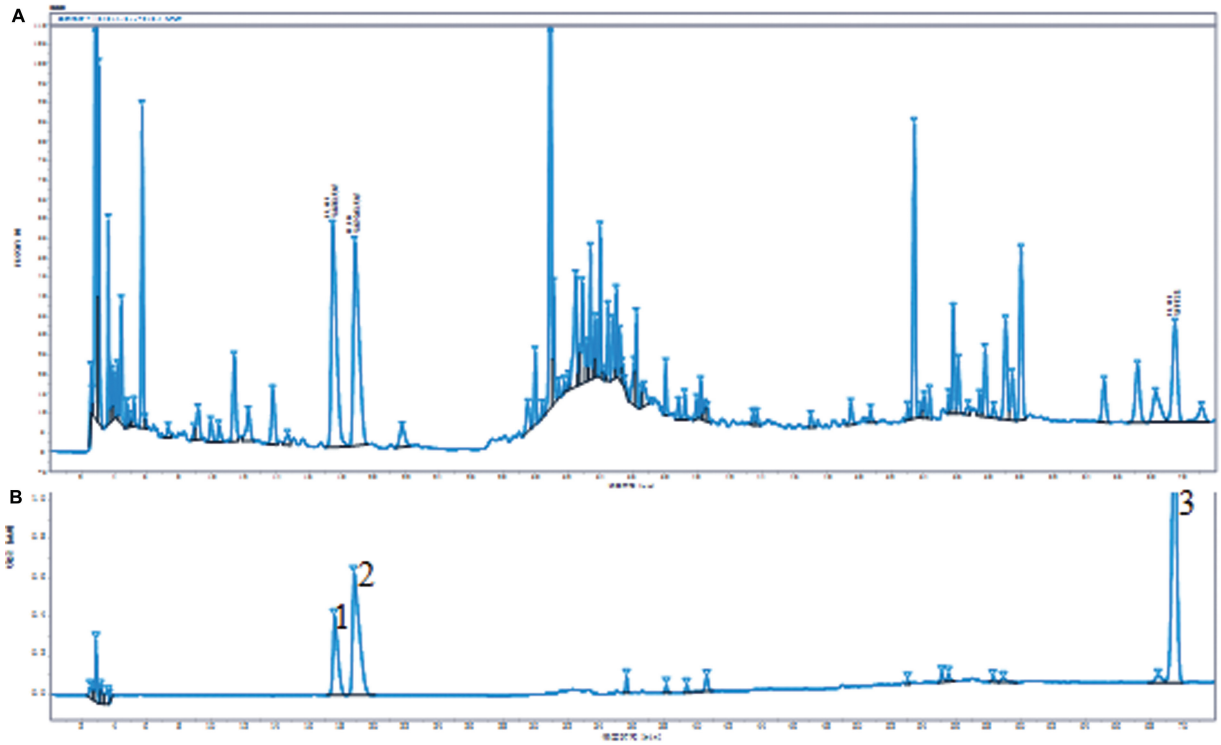

Fig. 1 Chromatogram.
Notes: A: Control solution; B: Test solution; 1: Ephedrine hydrochloride; 2: Pseudoephedrine hydrochloride; 3: Asarinin.

Method Validation

Accurately transfer 1, 3, 5, 7, 10, and 12 µL of the mixed control solution (in the section "Preparation of the Control Solution") into the chromatograph and investigate the linear relationship according to the chromatographic conditions in the section "Chromatographic Conditions." The linear equations are the following: (1) ephedrine hydrochloride: $Y = 13{,}188X - 5.4067$, $R^2 = 0.9999$; (2) pseudoephedrine hydrochloride: $Y = 11{,}110X + 16.758$, $R^2 = 0.9992$; and (3) asarone: $Y = 17{,}828X + 11.227$, $R^2 = 0.9997$. All three R^2 values are greater than 0.999, indicating a good linear relationship within the detection range. Accurately transfer 5 µL of the mixed control solution (in the section "Preparation of the Control Solution") and perform six injections consecutively. Conduct the instrument precision test according to the chromatographic conditions in the section "Chromatographic Conditions." The relative standard deviation (RSD) of the peak areas for ephedrine hydrochloride, pseudoephedrine hydrochloride, and asarinin were 0.34%, 0.31%, and 0.70%, respectively, all less than 3.0%, indicating good instrument precision. Accurately transfer the sample solution (in the section "Preparation of the Test Solution") and perform injections at 0, 2, 4, 6, 8, and 10 h. Conduct the solution stability test at room temperature according to the chromatographic conditions in the section "Chromatographic Conditions." The stability of ephedrine hydrochloride, pseudoephedrine hydrochloride, and asarone at room temperature over 10 h is reflected by RSD values of 0.99%, 2.04%, and 2.69%, respectively, all less than 3.0%, indicating good method stability. Accurately transfer 5 µL of the sample solution (in the section "Preparation of the Test Solution") and perform six injections for the repeatability test. The RSD values were all less than 3.0%, demonstrating good repeatability of the method. The recovery rates for ephedrine hydrochloride, pseudoephedrine hydrochloride, and asarone were 98.20%, 94.60%, and 92.40%, respectively, indicating that the sample preparation method meets the requirements.

Extraction Time Investigation

Weigh the medicinal herbs according to the prescribed dosage, then add 10 times the volume of water for extraction. Start timing when the water begins to boil and set the extraction time gradient as 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, and 4.5 h. Perform the extraction once and conduct three parallel experiments. The extract was analyzed for relevant indicator components according to the chromatographic conditions in the section "Chromatographic Conditions." The results showed that the content of the key components of Mahuang Xixin Fuzi decoction increased and then decreased with the extension of the extraction time. The optimal extraction time for Xixin's active ingredients was 1.5 h, and for Mahuang's active ingredients, it was 3 h. These results validate the scientific basis of traditional decoction methods. However, since the herbs require multiple extractions in later stages, and considering the total extraction time, the experimental extraction times were set at 0.5, 1.0, and 2 h. The results are shown in ►**Figs. 1** to **4**.

Yield Determination

Take three evaporation dishes that have been dried to constant weight, and accurately weigh them before drying

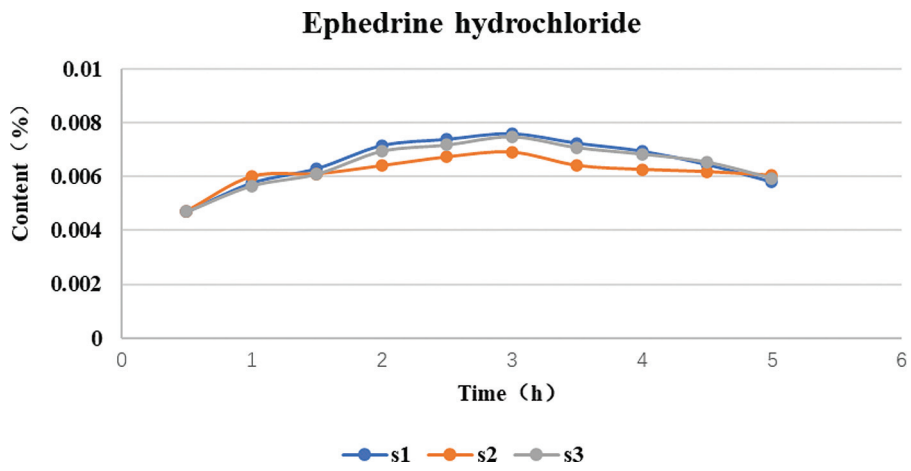

Fig. 2 Changes in the content of ephedrine hydrochloride over time.

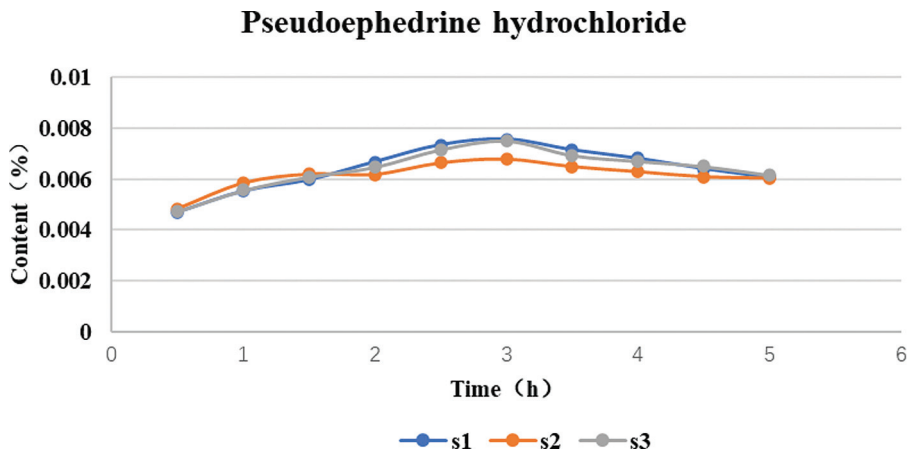

Fig. 3 Changes in the content of pseudoephedrine hydrochloride over time.

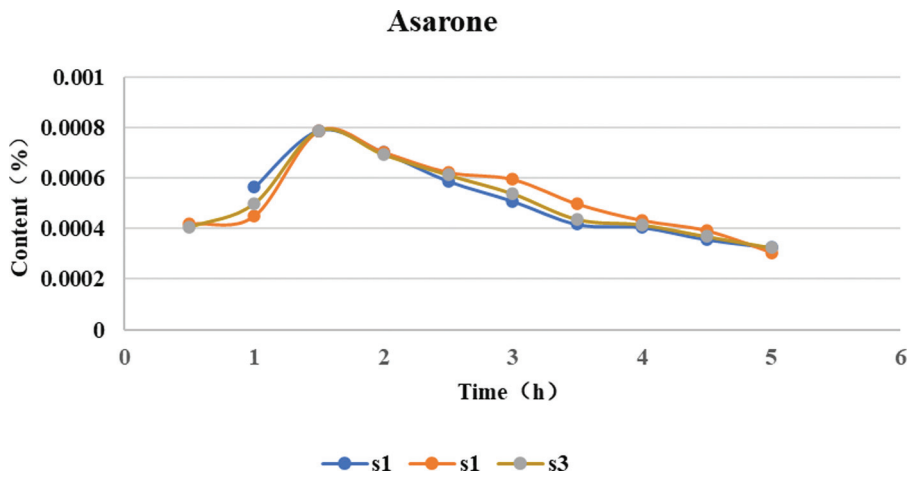

Fig. 4 Changes in the content of asarone over time.

and setting aside for use. Accurately transfer 25.00 mL of the control solution from the section "Preparation of the Standard Solution" into the evaporation dishes and evaporate to dryness in a water bath. Dry the samples at 105°C for 3 h, then cool them in a desiccator for 30 min. Weigh the dishes promptly and accurately. Each sample was measured three times, and the average value was recorded. The results are shown in ►**Table 1**.

Determination of Indicator Components

Weigh three portions of medicinal herbs according to the prescribed dosage. After extraction using the method in the

Table 1 Yield of extract and determination results of indicator components for Mahuang Xixin Fuzhi Decoction

No.	Ephedrine hydrochloride (mg/g)	Pseudoephedrine hydrochloride (mg/g)	Asarone (mg/g)	Dry extract yield/%
1	3.4237	3.3266	0.0510	9.96%
2	5.3318	5.3917	0.2609	16.04%
3	7.3198	7.3650	0.4790	19.63%
4	5.4596	5.2586	0.2771	15.9%
5	7.4959	6.7287	0.5726	19.39%
6	4.4984	4.5661	0.0917	12.99%
7	7.0453	6.7575	0.5340	19.22%
8	4.5448	4.2775	0.0986	12.26%
9	7.1059	6.8111	0.4670	19.52%

section "Preparation of the Standard Solution," take 10 mL of the extract, concentrate it in an evaporation dish, dissolve in methanol, and dilute to 10 mL. Determine the content of the indicator components, including ephedrine hydrochloride, pseudoephedrine hydrochloride, and asarone, according to the chromatographic conditions in the section "Chromatographic Conditions." Each sample was measured three times, and the average value was recorded. The results are shown in ►**Table 1**.

Orthogonal Experiment Design

Weigh the medicinal herbs according to the prescribed dosage and use a three-factor, three-level orthogonal experiment design. Based on the water volume used in traditional decoction methods and related literature,[15–22] the factors and their levels were set as follows: water volume (A): 8x, 10x, and 12x; extraction time (B): 0.5, 1, and 2 h; extraction times (C): 1, 2, and 3. The comprehensive evaluation indices for optimizing the extraction process included yield of extract, and transfer rate of indicator components. The transfer rate was calculated as follows: transfer rate = (content of extracted medicinal component × amount of extract)/(content of medicinal herb × amount of herb). The comprehensive evaluation score was calculated as follows: ephedra alkaloids/maximum ephedra alkaloids × 33.33 + asarone/maximum asarone × 33.33 + dry extract yield/maximum dry extract yield × 33.33.

Analysis of Variance

From ►**Table 2**, it can be seen that the highest comprehensive score is 98.54, corresponding to serial number 5. The range analysis indicates that the optimal levels are A2B2C3, with the primary and secondary relationships of the three factors being C > B > A. From the analysis in ►**Table 3**, it is clear that the amount of water added has the smallest effect on the extraction efficiency, while the number of extractions has the greatest impact. Based on the above analysis, the optimal extraction process is A2B2C3, which corresponds to adding 10 times the amount of water, extracting for 1 h, and performing three extractions.

Table 2

No.	Amount of water added	Extraction time(t/h)	Extraction times	Ephedra alkaloids (mg/g)	Asarone (mg/g)	Dry extract yield/%	Comprehensive score
1	8	0.5	1	6.7504	0.0510	9.96	39.10
2	8	1.0	2	10.7234	0.2609	16.04	70.74
3	8	2.0	3	14.6849	0.4790	19.63	97.67
4	10	0.5	2	10.7182	0.2771	15.9	71.46
5	10	1.0	3	14.2246	0.5726	19.39	98.54
6	10	2.0	1	9.0645	0.0917	12.99	52.47
7	12	0.5	3	13.8028	0.5340	19.22	96.77
8	12	1.0	1	8.8222	0.0986	12.26	48.73
9	12	2.0	2	13.9170	0.4670	19.52	92.32
*K*1	196.50	197.70	129.58				
*K*2	213.96	211.71	226.13				
*K*3	233.36	234.42	288.12				
R	12.39	12.34	52.85				

Table 3 Analysis of variance

Source of variation	Amount of water added	Extraction time(t/h)	Extraction times	Comprehensive score	Error	Total
Sum of squares of deviations	226.69	228.97	4,255.84	61.31	14.46	4,772.80
Degree of freedom	2.00	2.00	2.00	2.00	2.00	8.00
Mean square (MS)	113.34	114.48	2,127.92	30.65	7.23	
F value	15.68	15.83	294.32	4.24		
F critical value	$F_{0.01}(1,2) = 99$			$F_{0.05}(1,2) = 19$		

Three-Batch Validation Experiment

Parallel validation experiments were carried out in three parallel experiments according to the optimal extraction process. Specifically, three samples of herbs, each with the amount equivalent to one prescription, were taken, 10 times the amount of water was added, and the mixture was boiled for 1 h and extracted three times. The decoction was then combined and filtered. The content of key components and the extraction rate were measured according to the chromatographic conditions in the section "Chromatographic Conditions." The results showed that the method has a high extraction rate and good stability. The results are shown in ►**Table 4**.

Preparation of Mahuang Xixin Fuzi Decoction Granules

Investigation of the Relative Density of the Extract

Six portions of herbs were weighed according to the dosage, and the herbs were extracted using the optimal extraction process and concentrated into a thick extract. The viscosity of the extract was observed at different concentration ratios. The results showed that when the relative density of the concentrated liquid was less than 1.20 g/mL, the extract was liquid, had a high water content, and was not suitable for granulation. When the relative density was greater than 1.32 g/mL, the extract was too viscous, and the addition of excipients caused clumping, making granulation difficult. When the relative density was around 1.30 g/mL, the extract had moderate viscosity, making granulation easier. Therefore, the final determination of the extract's relative density was set to 1.30 g/mL (at room temperature).

Selection of Granulation Method

A preliminary experiment indicated that the extract obtained by traditional water decoction had high viscosity, making it unsuitable for dry granulation. Wet granulation, on the other hand, resulted in uniform granules with minimal loss of extract during the process and stable quality. Therefore, this study adopted wet granulation.

Selection of Excipients

Since the Mahuang Xixin Fuzi decoction extract is highly viscous and difficult to disperse, suitable excipients need to be added. Dextrin and starch are commonly used excipients in Chinese medicine granulation. Preliminary experiments revealed that dextrin increased the hardness and viscosity of the extract, causing it to clump and making it difficult to form soft materials. Additionally, the resulting granules were uneven with significant loss. Starch contributes to the formation of soft materials, but granules particles prepared with starch as an auxiliary material are loose and fragile, and there are many fine powders. Therefore, a mixture of the two was considered as the excipient. After examining the effects of different ratios of excipients on the pass rate of granules, hygroscopicity, and dissolution time, the final ratio of dextrin to starch was determined to be 1:2. The results are shown in ►**Table 5**.

Granulation Process Verification

With reference to the literature[23–28] and through preliminary experiments for comparison, a comprehensive analysis was conducted based on the formability, hygroscopicity, and solubility of the granules. The formability followed the regulations in the 2020 edition of the *Pharmacopoeia of China*, Part III, which stipulates that the total amount

Table 4 Validation test results

No.	Ephedrine hydrochloride content/%	Extraction rate of ephedrine hydrochloride/%	Pseudoephedrine hydrochloride content/%	Extraction rate of pseudoephedrine hydrochloride/%	Content of asarone/%	Extraction rate of asarone/%
1	0.7496	91.56	0.6729	86.62	0.0573	57.26
2	0.7557	92.30	0.6807	87.63	0.0577	57.73
3	0.7428	90.73	0.6653	85.65	0.0565	56.46
Mean	0.7494	91.53	0.6730	86.64	0.0571	57.15
RSD/%	0.8612	0.8612	1.1434	1.1434	1.1193	1.1193

Abbreviation: RSD, relative standard deviation.

Table 5 Excipients ratio investigation results

No.	Dextrin: starch	Pass rate/%	Hygroscopicity rate/%	Dissolution time (t/s)	Comprehensive score
1	1:2	96.92	10.82	72.28	97.96
2	1:3	92.80	10.66	76.02	95.33
3	1:4	89.42	10.16	84.31	92.61

passing through sieve nos. 1 and 5 should not exceed 15%.[29] Hygroscopicity was tested by accurately weighing an appropriate amount of granules and placing them in a previously dried and weighed flat-bottomed bottle. This was then placed in a desiccator containing a saturated sodium chloride solution (48 h) and sealed. After 24 h, the final weight was recorded.[25] Solubility was tested according to the 2020 edition of the *Pharmacopoeia of China*, Part III, which specifies that 10 g of the sample should be combined with 200 mL of heated water, stirred for 5 min, and immediately observed. Soluble granules should completely dissolve or become slightly turbid.

Verification experiments were conducted following the optimal granulation process. Three parallel experiments were performed, with formability, solubility, and hygroscopicity as the indicators. The RSD values for all three indicators were found to be less than 3.0%, indicating good stability of the granulation process. The results are shown in ►**Table 6**.

Discussion

Investigation of the Purification Process

Mahuang Xixin Fuzi decoction is a classic prescription, and during the study, traditional usage patterns were carefully considered. A decoction extraction method was employed to maximize the retention of the clinical efficacy of the original formula. During preliminary experiments, the purification process of the extract was also examined. The effects of purifying the extract with 30%, 50%, and 70% ethanol on the content of asarinin in the extract were investigated. It was found that 70% ethanol showed the most significant purification effect on asarinin, but it also affected the content of ephedrine hydrochloride and pseudoephedrine hydrochloride in the key herb, Mahuang (Ephedrae Herba). After considering various factors and adhering to the traditional prescription, no alcohol treatment was applied to the extract.

Table 6 Verification experiment results

No.	Granulation rate/%	Solution time (t/s)	Hygroscopicity rate/%
1	98.42	69.52	10.62
2	97.21	72.35	10.79
3	95.56	73.46	10.46
RSD/%	1.48	2.83	1.55

Abbreviation: RSD, relative standard deviation.

Investigation of the Extraction Process

The traditional decoction method involves first boiling Mahuang (Ephedrae Herba), followed by Fuzi (Aconm Lateralis Radix Praeparaia) and Xixin (Asari Radix et Rhizoma), with all three herbs boiled together for 3 h in a single decoction. In this study, the process was adjusted so that all three herbs were boiled simultaneously for three extractions. The content of key chemical components was measured, and it was found that there was no significant difference in the content of ephedrine hydrochloride and pseudoephedrine hydrochloride between the two extraction methods. Therefore, it was ultimately decided to boil the three herbs together for three extractions. In the later stages of the granulation process research, the decoction method for the reference substance solution was also adjusted, with Mahuang (Ephedrae Herba), Fuzi (Aconm Lateralis Radix Praeparaia), and Xixin (Asari Radix et Rhizoma) being decocted together.

Wetting Agent Study

Ethanol is commonly used as a wetting agent for the full tincture of traditional Chinese medicine. During the experiment, the effects of ethanol in different concentrations as a wetting agent were examined. The results indicated that 60% ethanol was the most suitable wetting agent. However, comparative studies found that when water and 60% ethanol were used as wetting agents, the difference of their granulation effects was not significant. Therefore, based on the principle of "green, economical, and safe" production, the extract was directly used to prepare the soft material and granules.

Excipient Ratio Study

In the study of excipient ratios, it was found that using dextrin or starch alone was not effective in preparing the soft material. Therefore, the impact of mixing both on the preparation of the soft material was investigated. The study found that when the ratio of dextrin to starch was 3:1 or 1:1, the soft material could not form, and significant caking occurred. This was presumed to be due to the high proportion of dextrin, which increased the viscosity of the soft material, leading to caking. After adjusting the dextrin-to-starch ratio, the effect of different ratios (1:2, 1:3, and 1:4) on the soft material preparation was tested. The optimal ratio was found to be 1:2.

Conclusion

This study optimizes the extraction process of Mahuang Xixin Fuzi decoction from multiple perspectives. The final

optimal extraction method for Mahuang Xixin Fuzi decoction is to simultaneously decoct Mahuang (Ephedrae Herba), Xixin (Asari Radix et Rhizoma), and Fuzi (Aconm Lateralis Radix Praeparaia), adding 10 times the amount of water, boiling for 1 hours, and extracting three times. The granulation process was examined using indicators of formability, solubility, and hygroscopicity. The optimal granulation process was determined to be using the extract of Mahuang Xixin Fuzi decoction with a relative density of 1.3 g/mL at room temperature, an excipient ratio of dextrin to starch of 1:2, and wet granulation. This study provides experimental support for the preparation and industrial production of Mahuang Xixin Fuzi decoction granules.

CRediT Authorship Contribution Statement

Lingli Cao was the project administration and contributed to conceptualization, data curation, formal analysis, and writing of the original draft. Congying Wang contributed to the investigation, data curation, formal analysis, validation, and methodology. Yinman Feng contributed to project administration, funding acquisition, supervision, and writing—review and editing of the manuscript.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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