FORMULATION DEVELOPMENT OF HARD CAPSULES CONTAINING ORTHOSIPHON STAMINEUS AND DESMODIUM STYRACIFOLIUM EXTRACTS

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ABSTRACT

Objective: To develop a hard gelatin capsule formulation containing dry extracts of Orthosiphon stamineus and Desmodium styracifolium and to evaluate selected preformulation characteristics, manufacturing conditions, and quality attributes of the finished capsules according to the Vietnamese Pharmacopoeia V.

Methods: Preformulation studies of the dry extracts were conducted, including evaluation of moisture content, hygroscopicity, flowability, and drug–excipient compatibility. Hard capsules were prepared using the wet granulation method, with investigations into appropriate binders, diluents, and lubricants. The quality attributes of intermediate products and finished capsules were evaluated according to the Vietnamese Pharmacopoeia V.

Results: The dry extract of Orthosiphon stamineus had a moisture content below 5%, showed hygroscopic characteristics, and exhibited very poor flowability (Carr's index approximately 35%). Wet granulation using 5% PVP in 96% ethanol as a binder, dicalcium phosphate as a diluent, and 1% talc as a lubricant significantly improved the flowability of granules (Carr's index approximately 15–18). Size 0 hard capsules had an average weight of approximately 500 mg and met the requirements for appearance, uniformity of mass, disintegration, and contents of rosmarinic acid and sinensetin.

Conclusion: The developed formulation and wet granulation process improved the physicochemical properties and flowability of the herbal extracts and produced hard gelatin capsules meeting selected pharmacopoeial quality requirements at laboratory scale. The findings provide preliminary evidence supporting further studies on dissolution, stability, and scale-up feasibility.

Keywords: Orthosiphon stamineus, Desmodium styracifolium, hard capsules, rosmarinic acid, sinensetin.

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I. INTRODUCTION

Urinary tract disorders, including nephrolithiasis, urolithiasis, urinary tract infections, and dysuria, have shown an increasing trend, particularly among adults and the elderly population. In addition to conventional synthetic drugs, the use of herbal-based preparations for the supportive treatment and prevention of these conditions has gained increasing attention due to their safety profile, lower incidence of adverse effects, and suitability for long-term use.

Orthosiphon stamineus Benth. (family Lamiaceae), commonly known as "Râu mèo," is a medicinal plant widely used in both traditional and modern medicine for its diuretic effects, promotion of uric acid excretion, and supportive role in the prevention and treatment of kidney and urinary stones. Previous studies have demonstrated that Orthosiphon stamineus contains various bioactive compounds, including flavonoids, rosmarinic acid, and sinensetin, which exhibit diuretic, anti-inflammatory, and antioxidant activities. Desmodium styracifolium ("Kim tiền thảo") is commonly combined with Orthosiphon stamineus in traditional herbal formulations. It possesses choleretic and diuretic effects, supports the dissolution of urinary calculi, and enhances stone excretion. The combination of these two medicinal plants is believed to exert synergistic effects in the management of urinary tract disorders.

Currently, various preparations containing Orthosiphon stamineus and Desmodium styracifolium are available on the market, including decoctions, liquid extracts, and herbal teas. However, these dosage forms present several limitations, such as bulky dosing, difficulties in storage, variability in active constituent content, and inconvenience in administration. In contrast, hard gelatin capsules represent a modern dosage form with several advantages, including masking of unpleasant taste and odor, ease of administration, dose standardization, and improved convenience for patients [1], [2].

The formulation of hard gelatin capsules from dried herbal extracts presents significant technological

challenges, as such extracts are often hygroscopic, exhibit poor flowability, and tend to agglomerate, thereby affecting encapsulation efficiency and product quality. Therefore, preformulation studies and the selection of appropriate manufacturing processes and excipients are essential to ensure that the final product meets the quality requirements of the Vietnamese Pharmacopoeia V.

II. MATERIALS AND METHODS

2.1. Materials and Equipment

Materials:

Solvents and chemicals used for analysis, including acetonitrile, methanol, and ethanol, were of analytical grade (P.A.) and high-performance liquid chromatography grade (HPLC grade). Excipients such as microcrystalline cellulose (Avicel), cassava starch, lactose, dicalcium phosphate, talc, magnesium stearate, sodium starch glycolate, croscarmellose sodium, and crospovidone complied with pharmaceutical-grade standards.

Equipment:

High-performance liquid chromatography (HPLC) system (Shimadzu), capsule filling machine, manual capsule filling device, drying oven, and analytical balance.

Other laboratory apparatus:

Standard sieves of various mesh sizes, volumetric flasks, and general glassware used in the laboratory.

2.2. Preformulation Studies

The physicochemical properties of the dried extract of Orthosiphon stamineus were evaluated prior to the formulation of hard gelatin capsules. The investigated parameters included moisture content (Appendix 9.6, Vietnamese Pharmacopoeia V), hygroscopicity (Appendix 5.11, European Pharmacopoeia 10), bulk density, and flow properties of the powder mass (Appendix 11, Vietnamese Pharmacopoeia V).

In addition, during the manufacturing process of hard gelatin capsules, the dried extract is inevitably exposed to elevated temperatures as well as to various excipients commonly used in capsule formulation. Therefore, the stability of the dried extract of Orthosiphon stamineus was assessed under drying conditions (50–65°C), and drug–excipient compatibility studies were conducted with commonly used excipients, including microcrystalline cellulose (Avicel), cassava starch, lactose, dicalcium phosphate, talc, magnesium stearate, sodium starch glycolate, croscarmellose sodium, and crospovidone [3].

To evaluate the extent of interactions, the contents of rosmarinic acid and sinensetin were quantified using a high-performance liquid chromatography with diode-array detection (HPLC-DAD) method under the following analytical conditions:

- Stationary phase: C18 column (250 × 4.6 mm, 5 µm)
- Detection wavelength: 320 nm
- Injection volume: 10 µL
- Column temperature: 25°C
- Flow rate: 1.5 mL/min
- Mobile phase: Water containing 0.1% formic acid (channel A) and acetonitrile (ACN, channel B), with a gradient elution program as follows:

Time (min)	Channel A (%)	Channel B (%)
0 – 25	95 – 50	5 – 50
25 – 26	50 – 20	50 – 80
26 – 35	20 – 95	80 – 5
35-45	95	5

2.3. Formulation Development of Hard Gelatin Capsules

Following the evaluation of the physicochemical properties of the dried extracts, the wet granulation method was selected for the preparation of hard gelatin capsules. The formulation development process was carried out according to the following steps [4]:

Capsule size determination

To fill the formulation into capsules, an appropriate capsule size must first be selected based on the required fill weight of the active ingredients. The capsule size was determined according to the following equation:

$m = D * V$

Where:

m is the mass of the fill material (capsule content);

D is the bulk density of the powder;

V is the capsule volume.

Excipient selection

- **Disintegrants:** Sodium starch glycolate, croscarmellose sodium, and crospovidone were investigated.

- Diluents (fillers): Lactose, cassava starch, and dicalcium phosphate were evaluated.

- Binders: Ethanol 96%, ethanol 70%, 5% (w/v) polyvinylpyrrolidone (PVP) solution in 96% ethanol, and 7% (w/v) PVP solution in 96% ethanol were investigated.

- Lubricants: Talc and magnesium stearate were evaluated.

Development of capsule filling method at a scale of 300 capsules/batch

The manufacturing process of capsules containing dried extracts of Orthosiphon stamineus and Desmodium styracifolium includes the following steps:

- Weighing and sieving of materials, including dried extracts of *Orthosiphon stamineus*, dried extracts of *Desmodium styracifolium*, and dicalcium phosphate (sieved through a 0.25 mm mesh), talc, and magnesium stearate (sieved through a 0.18 mm mesh).

- Preparation of binder: PVP-K30 was dissolved in 96% ethanol.

- Dry mixing: the dried extracts of Orthosiphon stamineus and Desmodium styracifolium were blended with dicalcium phosphate according to the geometric dilution method, followed by the addition of 5% PVP solution in 96% ethanol to form a wet mass. The wet mass was granulated through a 1 mm sieve and dried at 60°C until the moisture content was below 5%. The obtained granules were then mixed uniformly with lubricants.

- Filling the powder into size 0 capsules, cleaning residual powder from the capsule shells, and packaging.

Evaluation of the quality of capsule granules (intermediate product) and hard gelatin capsules [4]

Evaluation of the effects of formulation components on granule quality based on the following criteria:

- Appearance: evaluated by visual inspection

- Moisture content: determined by loss on drying method according to Appendix 9.6, Vietnamese Pharmacopoeia V

- Granulation yield: ratio of the mass of granules after sizing to the initial total powder mass

- Percentage of particles with size < 0.25 mm: 20 g of granules were sieved, and the mass fraction passing through the sieve was calculated relative to the total granule mass

- Bulk density: determined by volume measurement using a graduated cylinder according to Appendix 6.13, Vietnamese Pharmacopoeia V

Evaluation of hard gelatin capsules quality

- Appearance: visually examined under natural light

- Moisture content: granules were removed from capsules and determined by the loss on drying method according to Vietnamese Pharmacopoeia V

- Uniformity of mass: according to Appendix 11.3, Vietnamese Pharmacopoeia V

- Disintegration: according to Appendix 11.6, Vietnamese Pharmacopoeia V

- Assay: determination of rosmarinic acid and sinensetin contents using HPLC-DAD

2.4. Research ethics

The study was conducted using herbal materials and pharmaceutical excipients without the involvement of human subjects or experimental animals. All experimental procedures complied with laboratory safety regulations and the requirements of the Vietnamese Pharmacopoeia V. The study was approved by the Ministry of Health under Decision No. 1652/QD-BYT dated June 24, 2022.

III. RESULTS

3.1. Preformulation Studies

Moisture content: Moisture content was evaluated across three batches of raw materials. The moisture content of the dried extract of Orthosiphon stamineus was 4.83 ± 0.08%. This value complies with the requirements specified in the monograph for powdered materials in the Vietnamese Pharmacopoeia V, indicating its suitability for pharmaceutical use.

Hygroscopicity: Hygroscopicity was assessed at 25°C and 80% relative humidity. The results showed that the mass of the dried extract increased by 9.26 ± 0.17%, indicating that the extract is hygroscopic. Therefore, the extract should be processed and stored under low-humidity conditions, and moisture-absorbing excipients should be considered.

Bulk density and flowability (Carr's index): Determined using the graduated cylinder method, the tapped density was 0.92 ± 0.01 g/mL, and the bulk density was 0.52 ± 0.01 g/mL, resulting in a Carr's index of 34.75 ± 1.91. This value indicates poor flowability of the powder, which may affect mass and content uniformity of the capsules. Therefore, wet granulation and the addition of lubricants were prioritized in the formulation process.

Effect of temperature (50–65°C) on stability: The stability of the dried extract of *Orthosiphon stamineus* was evaluated under drying temperatures ranging from 50 to 65°C. After 24 hours, the recovery of rosmarinic acid and sinensetin remained above 98%, indicating good stability of the extract under these conditions.

Drug–excipient compatibility: The compatibility of the dried extract with commonly used excipients (Avicel, cassava starch, lactose, dicalcium phosphate, talc, magnesium stearate, sodium starch glycolate, croscarmellose sodium, and crospovidone) was investigated at 60°C for two weeks. The results showed that the recovery of rosmarinic acid and sinensetin remained above 98%, indicating no significant interaction between the extract and the tested excipients. Therefore, these excipients were selected for further formulation development.

3.2. Formulation Development at Laboratory Scale (300 capsules/batch)

3.2.1. Capsule size determination

The expected amount of dried extract of Orthosiphon stamineus per capsule (>20%) was 200 mg. With a density ranging from 0.52 to 0.92 g/mL, the corresponding volume per capsule was estimated to be 0.22–0.38 mL. Based on this density range, the standardized extract is suitable for capsule sizes 0 (0.67 mL) and 1 (0.48 mL). However, each capsule also contains 200 mg of dried extract of Desmodium styracifolium. Therefore, size 0 capsules were selected to accommodate the combined extracts. For size 0 capsules (volume 0.67 mL), the target fill weight was estimated to be approximately 480–520 mg per capsule.

3.2.2. Excipient selection

Investigation of binder types: Wet granulation was performed using a mixture of dried extracts of Orthosiphon stamineus and Avicel (formulation equivalent to 100 capsules, corresponding to 20.0 g of Orthosiphon stamineus extract, 20.0 g of Desmodium styracifolium extract, and 10.0 g of Avicel, equivalent to 500 mg per capsule) with 20% (v/w) of different binders. The results of binder selection are presented in the following table.

Table 1. Effect of binder type on granulation yield (formulation for 100 capsules)

Batch / Components	B1	B2	B3	B4
Dried extract of Orthosiphon stamineus (g)	20,0	20,0	20,0	20,0
Dried extract of Desmodium styracifolium (g)	20,0	20,0	20,0	20,0
Avicel	9,0	9,0	9,0	9,0
EtOH 96 % (ml)	10			
EtOH 70 % (ml)		10		
3% PVP/ EtOH 96% (ml)			10	
5% PVP/ EtOH 96% (ml)				10
Appearance	Black color, relatively uniform particle size distribution	Black color, non-uniform particle size distribution, tendency to liquefy	Black color, relatively uniform particle size distribution	Black color, non-uniform particle size distribution

Batch / Components	B1	B2	B3	B4
Processing characteristics	Easy to form a wet mass, easy to granulate	Severe agglomeration, unable to granulate	Easy to form a wet mass, difficult to granulate	Easy to form a wet mass, difficult to granulate
Granulation yield (%)	94,5%	64,4%	92,6%	91,8%
Percentage retained on 0.25 mm sieve (%)	73,3%	95,8%	83,8%	88,5%

Remarks: It was observed that formulation B1 exhibited the highest granulation yield; however, the obtained granules were not sufficiently firm and were prone to breakage. In formulation B4, with the addition of 5% PVP in 96% ethanol, the resulting granules were firm, and the percentage of particles retained on the 0.25 mm sieve was relatively high (88.5%). Therefore, 5% PVP in 96% ethanol was selected as the binder for subsequent formulations.

• **Investigation of diluents** The use of diluents may improve granulation yield and increase the percentage of particles retained on the 0.25 mm sieve. Several diluents, including lactose, Avicel, cassava starch, and dicalcium phosphate, were evaluated. The granulation performance in the presence of these excipients was assessed. The results of the diluent study are presented in the following table.

Table 2. Results of the investigation on the effect of diluents

Formulation / Components	A1	A2	A3	A4
Dried extract of *Orthosiphon stamineus* (g)	20,0	20,0	20,0	20,0
Dried extract of *Desmodium styracifolium* (g)	20,0	20,0	20,0	20,0
Avicel	9,0			
EtOH 96 % (ml)		9,0		
EtOH 70 % (ml)			9,0	
3% PVP/ EtOH 96% (ml)				9,0
5% PVP/ EtOH 96% (ml)	10	10	10	10
Appearance	Black color, non-uniform particle size distribution	Black color, relatively uniform particle size distribution	Black color, relatively uniform particle size distribution	Black color, relatively uniform particle size distribution
Processing characteristics	Easy to form a wet mass, prone to agglomeration	Easy to form a wet mass, easy to granulate	Easy to form a wet mass, easy to granulate	Easy to form a wet mass, easy to granulate
Granulation yield (%)	72,37%	92,41%	88,74%	92,74%
Percentage retained on 0.25 mm sieve (%)	91,46%	83,51%	81,37%	81,37%
Bulk density (g/mL)	0,61	0,52	0,55	0,65

Remarks: Lactose exhibited poor moisture uptake, resulting in difficulty in granulation and drying of granules. Avicel and starch showed good hygroscopicity, facilitated granulation, and enabled rapid drying; however, the resulting granules had low bulk density. Dicalcium phosphate demonstrated good moisture uptake, ease of granulation, and produced granules with relatively high bulk density. Therefore, formulation A4, using dicalcium phosphate as the diluent, was selected for further formulation.
• Investigation of disintegrants The disintegrants, including sodium starch glycolate, croscarmellose sodium, and crospovidone, were evaluated at a concentration of 5% (w/w), with the following results:

Table 3. Results of the effect of lubricants

Components	R1	R2	R3	R4
Dried extract of *Orthosiphon stamineus* (g)	20,0	20,0	20,0	20,0
Dried extract of *Desmodium styracifolium* (g)	20,0	20,0	20,0	20,0
Dicalci phosphat	9,0	9,0	9,0	9,0
5%PVP/ethanol 96%	10,0	10,0	10,0	10,0
Sodium starch glyconat (g)		2		
Sodium croscarmellose (g)			2	
Crospovidon (g)				2
Disintegration time (min)	<10p	<10p	<10p	<10

Remarks: The disintegrants did not significantly affect the disintegration time of the capsules. This may be explained by the properties of the dried extract of Orthosiphon stamineus and the granulation method (using 5% PVP in 96% ethanol), which produced porous granules that readily dispersed in water. Therefore, disintegrants were not included in the final formulation.

• **Investigation of lubricants** To evaluate the flowability of the extract after wet granulation, the extract was granulated with the diluent (dicalcium phosphate) and binder (5% PVP in 96% ethanol), and the Carr's index was determined as follows:

Table 4. Carr's index before and after wet granulation

Sample	Carr's index before granulation	Carr's index after granulation
Lot H1	33,9	22,94
Lot H2	34,6	21,61
Lot H3	36,5	21,67

Remarks: It was observed that the wet granulation process significantly improved the Carr's index, shifting from very poor flowability to an acceptable level. However, it was considered that this improvement may still be insufficient for large-scale industrial production; therefore, lubricants were further incorporated to enhance flowability. The results obtained are as follows:

Table 5. Carr's index before and after the addition of lubricants

Sample	Tapped density ($d_{tapped)}$ (g/ml)	Carr's index without lubricants	Carr's index with lubricants (0.5% talc, 0.5% magnesium stearate)	Carr's index with lubricants (1% talc, 1% magnesium stearate)	Carr's index with lubricants (2% talc)
Lot H1	0,65	22,11	21,09	18,01	15,21
Lot H2	0,63	21,52	20,89	17,64	14,74
Lot H3	0,62	21,24	20,02	17,14	15,05

Remarks: It was observed that the Carr's index values after the addition of lubricants were at a moderate level (with 1% talc and 1% magnesium stearate) and at a good level (with 2% talc). Therefore, the formulation containing 1% talc and 1% magnesium stearate was selected as the lubricant system. The bulk density of the granules after wet granulation was 0.65 g/mL, corresponding to approximately 500 mg per size 0 capsule (0.67 mL). Accordingly, for capsules containing 200 mg of dried extract of Orthosiphon stamineus with a target fill weight of 500 mg per capsule, the formulation was established as follows:

Component	Amount
Dried extract of *Orthosiphon stamineus*	200 mg
Dried extract of *Desmodium styracifolium*	200 mg
Dicalcium phosphate	90 mg
Talc	5 mg
Magnesium stearate	5 mg
5% PVP in 96% ethanol	0.1 mL

3.2.3. Evaluation of quality attributes of Orthosiphon stamineus hard gelatin capsules

After preparation, the quality of the obtained hard gelatin capsules was evaluated with the following results:

Appearance: hard gelatin capsules, size 0; granules inside the capsules were black in color.

Uniformity of mass: the average weight of 20 capsules was 508.8 mg, and the mean weight deviation was less than 7.5%, complying with the requirements for uniformity of mass according to the Vietnamese Pharmacopoeia V.

Disintegration: the average disintegration time of 6 capsules was 7.5 minutes ± 8.5%, which is less than 30 minutes. Thus, the capsules met the disintegration requirements of the Vietnamese Pharmacopoeia V.

Assay: determination of rosmarinic acid and sinensetin contents in the capsules using the HPLC-DAD method.

Table 6. Content of rosmarinic acid and sinensetin in capsules

No	Capsule weight (g)	acid rosmarinic		sinensetin	
		Concentration (ug/ml)	Content (mg)	Concentration (ug/ml)	Content (mg)
1	0,5011	20,7506	2,0751	6,2688	0,6269
2	0,5002	21,0684	2,1068	5,9174	0,5917
3	0,4992	20,5820	2,0582	6,0553	0,6055
4	0,5021	19,8430	1,9843	5,7591	0,5759
5	0,5014	21,5652	2,1565	6,1422	0,6142
6	0,4996	20,5286	2,0529	6,0252	0,6025
Mean (mg)		2,0723		0,6027	
RSD (%)		2,78		2,93	

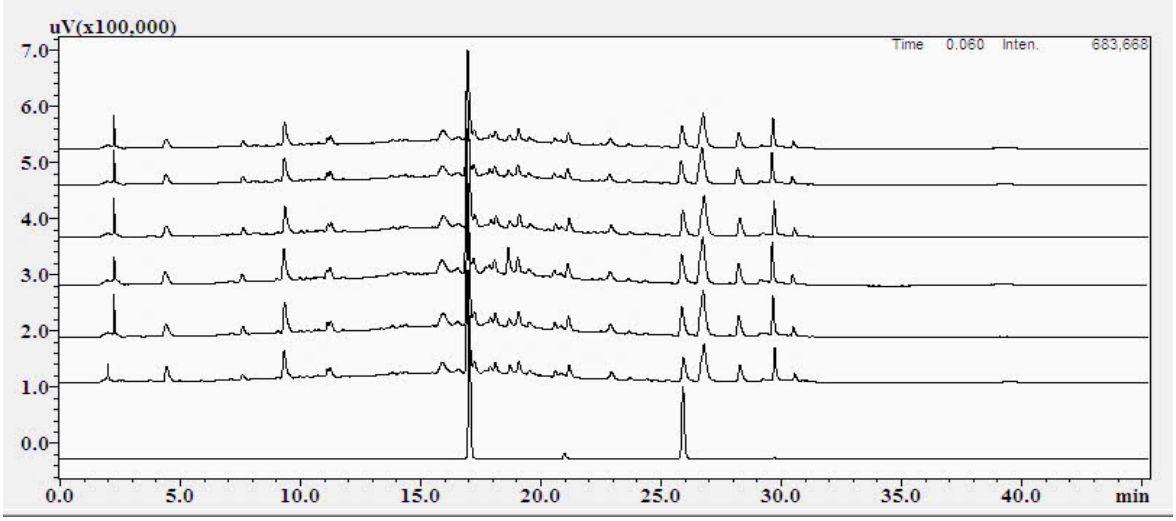

Figure 1. Chromatograms of the mixed standard solution of rosmarinic acid and sinensetin and six capsule samples

IV. DISCUSSION

The results of this study demonstrated that the formulation of hard gelatin capsules containing dried extracts of Orthosiphon stamineus in combination with Desmodium styracifolium was strongly influenced by the physicochemical properties of the herbal extracts, particularly their poor flowability and high hygroscopicity, which represent the main limiting factors. These characteristics pose challenges for direct capsule filling. This observation is consistent with the general properties of herbal extracts rich in flavonoids and polyphenols, which tend to exhibit cohesiveness and poor dispersibility.

The application of wet granulation instead of direct blending significantly improved the physical properties of the powder mass. The use of 5% PVP in 96% ethanol as a binder facilitated the formation of robust granules, reduced moisture uptake, and ensured uniform distribution of active constituents. Dicalcium phosphate was selected as a diluent and moisture-absorbing excipient; due to its relatively high density and low hygroscopicity, it contributed to enhancing the flowability of the granules. As a result, the Carr's index decreased to approximately 15–18%, which is suitable for stable capsule filling.

The final hard gelatin capsules met the requirements for appearance, uniformity of mass, disintegration, and content of the marker compounds, namely rosmarinic acid and sinensetin. These findings provide a preliminary basis for the development of standardized herbal capsule formulations. Further studies on dissolution, stability, and microbial quality are required to confirm the long-term quality of the developed formulation.

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