CHRONIC COUGH TREATMENT USING MODERN FORMULATION OF THE VIETNAMESE TRADITIONAL COUGH-RELIEVING REMEDY "BAI BU BU FEI TANG"

Bac Vu-Giang Nguyen[1], Thanh-Hoa Vo[2,3], Phuoc-Vinh Nguyen[2,3]

ABSTRACT

In tropical countries like Vietnam, due to the geographical conditions, the cough is one of the commonest diseases. Current cough treatments rely mainly on the use of chemical-synthesized drugs, which present several disadvantages due to a the drug resistance phenomenon, allegy and occasional side effects. Therefore, developing of a safe and effective strategy for cough treatment is in an urgent need. Among protential alternatives, traditional medicine is drawing an increasing attention from the scientific community because of its therapeutic efficacy and safety. Therefore, this study was performed to develop a novel formulation of "Bai Bu Bu Fei Tang" for treatment of chronic cough in Vietnam, comprising of *Radix Stemonae*, *Radix platycodi*, *Radix Ophiopogonis japonica*, *Radix et Rhizoma Glycyrrhizae*, *Fructus Terminaliae chebulae* and *Herba Pouzolziae zeylanicae*.

Keywords: *Bai Bu Bu Fei Tang, cough-relieving lozenge, modernization of traditional medicine.*

I. INTRODUCTION

In 2016, the Vietnam National Institute of Medical Materials reported a catalogue of 5,117 medicinal herbs each recognized for its therapeutic properties, highlighting the vast repository of natural resources underpinning Vietnamese Traditional Medicine. Fueled by the trend of "back to nature", the traditional medicine has witnessed a surge in usage, owing to its efficacy and minimized adverse side effects [1]. Coughing serves as a crucial physiological mechanism for clearing the airways. Working in tandem with the body's mucus system, it facilitates the expulsion of mucus from the respiratory tract and helps thwart the invasion of pathogens [2-4]. Nonetheless, cough symptoms often substantially impact patients' quality of life [4]. In addition to Western medicines, the utilization of Traditional Medicine remedies for cough management has expanded increasing attention in the scientific community [5-7]. Amongst different Vietnam traditional remedies for cough relieving, the "Bai Bu Bu Fei Tang" remedy, comprising *Radix Stemonae*, *Radix platycodi*, *Radix Ophiopogonis japonica*, *Radix et Rhizoma Glycyrrhizae*, *Fructus Terminaliae chebulae*, and *Herba Pouzolziae zeylanicae*, is a common and widely used one in Vietnam. However, the application of this potential cough-relieving remedy relies mainly on its traditional dosage forms, such as liquid extracts and syrups. Such preprations present several drawbacks, including unpleasant odor and taste, high volume consumption (from 50 to 150 mL per dose unit), inaccurate dosing, low stability and incompatibility towards diabetic patients [8-10].

[1] *Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City*
[2] *University of Health Sciences, Vietnam National University Ho Chi Minh City*
[3] *Research center of discovery and development of healthcare products, Vietnam National University Ho Chi Minh City*
Responsible person: Phuoc-Vinh Nguyen
Email: npvinh@uhsvnu.edu.vn
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To overcome these limitations and to improve the usage conveniency of this local traditional remedy, modern dosage forms such as compressed lozenges provide important benefits i.e. precise dosing, better swallowability, longer oral retention, higher stability, and sustained local therapeutic action [9, 11-13]. Additionally, the incorporation of a calorie-free sweetener makes this treatment more accessible to a wider range of patients, such as those with diabetes [9, 14]. This study was conducted to develop a cough-relieving lozenge formulation derived from the Vietnamese traditional remedy " Bai Bu Bu Fei Tang" to maximize the utilization of this promising Vietnamese traditional remedy.

MATERIALS AND METHODS

2.1. Plant materials

Vietnamese traditional remedy "Bai Bu Bu Fei Tang" includes 6 types of medicinal herbs: *Radix Stemonae*, *Radix platycodi*, *Radix Ophiopogonis japonica*, *Radix et Rhizoma Glycyrrhizae*, *Fructus Terminaliae chebulae*, and *Herba Pouzolziae zeylanicae*. These medicinal herbs subjected to various testing procedures outlined in the monographs specified within the Vietnamese Pharmacopoeia V [15]. Standard samples were provided by the Institute for Drug Quality Control (IDQC) Ho Chi Minh City (Viet Nam) and the National Research Institute of Chinese Medicine (Taiwan).

2.2. Excipients

Mannitol, aspartame, sodium saccharin, magnesium stearate (Mg stearate), menthol, lactose monohydrate (LM), corn starch, acesulfame K, avicel, aerosil, povidone K30, and peppermint essential oil were provided by Boston Pharma Vietnam, Ho Chi Minh City, Vietnam and met the pharmaceutical grade.

2.3 Extraction of herbal plants

Raw herbs were processed to a fragment size compatible with the extraction apparatus, similar to traditional methods of herb preparation. Subsequently, they were extracted in water with a ratio of 5:1 (w/w). The mixture was heated and maintained at a temperature of around 80 °C for two hours. Subsequently, the obtained mixture was filtered and the liquid phase was collected. This extraction step was repeated twice in order to obtain most of active compounds. The collected liquids were then concentrated at 80 °C until achieving an extract with water content around 20%. The quality assessment of the concentrated extract complied with the standards indicated in the Vietnamese Pharmacopoeia V monographs [15].

2.4. Preparation of compressed lozenges

The wet granulation process was chosen to prepare the compressed lozenges from the concentrated extract. Essential types of excipients, including diluents, binders, glidants, sweeteners, and flavoring agents were investigated.

2.5. Antimicrobial activity investigation

The disk diffusion method was utilized to assess the *in vitro* antimicrobial activity of the concentrated extract and the compressed lozenge against Methicillin-susceptible *Staphylococcus aureus* (MSSA) strain at the concentration of 100 mg/mL of dry extract.

III. RESULTS AND DISCUSSION

3.1. Specifications for raw medicinal herbs

The "Bai Bu Bu Fei Tang" remedy, consisting of *Radix Stemonae*, *Radix platycodi*, *Radix Ophiopogonis japonica*, *Radix et Rhizoma Glycyrrhizae*, *Fructus Terminaliae chebulae*, and *Herba Pouzolziae zeylanicae*, was assessed in accordance with the corresponding standards outlined in the

Vietnamese Pharmacopoeia V [15]. The findings, as delineated in Table S1, affirmed the adherence of the raw medicinal herbs to quality standards encompassing microscopical characteristics of plant part and powdered herbal substances, water content, total ash, ash insoluble in hydrochloric acid, impurities, assay, and extractable matter. These results unequivocally underscored the commendable quality of the procured raw medicinal herbs, thereby paving the way for subsequent research endeavors.

3.2. Specifications for herbal preparations

Following the extraction procedure, a total of 14.85 liters of liquid extracts was derived from 1.2 kilograms of raw medicinal herbs. Subsequently, the collected liquids underwent a concentration process at 80 °C until reaching an extract with a water content of approximately 20%. The resultant concentrated extract exhibits desirable characters and water soluble extractive, adhering to established quality standards. Furthermore, heavy metal residues were acceptable and pesticide residues with no indication of contamination, as elucidated in Table 1. With its confirmed quality, the concentrated extract is deemed suitable for advancing research endeavors aimed at formulating further preparations.

Table 1: ***Specifications for concentrated extracts***

Specifications	Results
Water soluble extractive	Pass
Characters	Pass
Loss on drying (%)	14.4 ± 0.19
Identification	Pass
Heavy metal residues - The amount of lead - The amount of arsenic - The amount of mercury	 0.015 ppm 0.010 ppm 0.005 ppm
Pesticide residues (methidathion, endosulfan, cypermethrin, dicofos, fenitrothrin, fipronil, propargit)	Undetected
Microbial limits - The Total Aerobic Plate Count - Total viable count for fungi - *Enterobacteriaceae* and certain other Gram-negative bacteria - *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella* spp.	Undetected Undetected Undetected Undetected

3.3. Preparation of compressed lozenges

Screening of diluents

Initially, diluents such as corn starch, lactose monohydrate (Lac), and mannitol (Man) were evaluated in combination with concentrated extract containing approximately 10% water content. The data indicated that corn starch, owing to its hydrophobic nature, is unsuitable as a diluent due to its inability to facilitate granulation. Conversely, lactose monohydrate and mannitol exhibit granulation capability, with an optimal concentrated extract to diluent ratio of 1:3. However, the granulation process proved to be a challenge resulting in granules of high hardness. This phenomenon may be attributed to the excessively low water content in the concentrated extract.

Table 2: ***Survey of diluents in lozenge formulations.***

Attributes	SE:Lac (1:4)	SE:Man (1:4)	SE:Lac:Man (1:1:3)
Water content	3.45%	2.92%	2.47%
The angle of repose α	35°	31°	30°
Hausner ratio	1.23	1.278	1.11
Carr index	21.0%	21.7%	10.3%

Following testing with concentrated extract containing 15% water content, granules formulated with lactose monohydrate (SE:Lac = 1:4) exhibit poor flowability, as evidenced by an angle of repose (α) of 35°. Attempts to enhance the flowability of these granulated powders through the addition of glidants such as avicel and aerosil proved ineffective. Nonetheless, these granulated powders demonstrated a notable advantage in their low moisture absorption capacity. Conversely, granulated powders prepared with mannitol (SE:Man = 1:4) displayed improved flowability (α = 31°) but exhibited pronounced hygroscopic tendencies. To mitigate hygroscopicity while maintaining adequate flowability, a combination of lactose monohydrate and mannitol (SE:Lac:Man = 1:1:3) was employed. Results revealed that this blend yielded granules that met predefined criteria for hygroscopicity, angle of repose (α), and Hausner ratio. Particularly noteworthy was the Carr index, which decreased by more than half (10.3%) compared to granules comprising single diluents (Table 2). Exhibiting favorable flow properties without succumbing to hygroscopic behavior, granulated powders formulated with this dual diluent combination were deemed optimal. Consequently, the ratio of concentrated extract (15% water content) to lactose monohydrate to mannitol at 1:1:3 was selected as the filler component for the formulation.

Screening of binders

The study on binders encompasses two key elements: delineating the binder addition procedure and identifying the optimal binder ratio. Findings indicated that granules produced via Process B exhibit superior flow properties compared to those generated by Process A. Notably, granules from Process B demonstrated minimal fines, along with expedited processing and reduced equipment requirement compared to Process A. Consequently, Process B was selected for further investigation, closely aligning with the targeted rate of adhesive excipients.

Table 3: ***Survey of the binder addition procedure in lozenge formulations.***

Attributes	Process A	Process B
Water content	2.98%	3.37%
The angle of repose α	30°	27°
Hausner ratio	1.14	1.06
Carr index	12.0%	4.0%
Amount of fines	Many	Few

The investigation into the PVP K30 binder rate was conducted at concentrations of 0.10%, 0.25%, and 0.50%. Findings revealed that increasing the binder percentage progressively enhanced the smooth granules, as illustrated in Table 3.4. It's particularly noteworthy that the Carr index significantly reduces, achieving a

minimum value of 4.50% at a PVP K30 concentration of 0.50%, which is also accompanied by a notable decrease in fines. In addition, even at a very low concentration (0.50%), the incorporation of PVP K30 ensures the formation of granules, likely attributed to the adhesive properties of sugars and mucilages present in the concentrated extract. These results suggest that the optimal binder ratio for the formulation is 0.50% PVP K30.

Table 4: ***Survey of the percentage of PVP K30 in compressed lozenge formulations.***

Percentage of binder	0.10%	0.25%	0.50%
Water content	2.39%	2.61%	2.47%
The angle of repose α	30°	30°	29°
Hausner ratio	1.13	1.18	1.05
Carr index	11.76%	15.20%	4.50%
Amount of fines	Many	Many	Few

Screening of glidants, flavoring agents and sweeteners

The evaluation of magnesium stearate glidants was carried out at concentrations of 0.1%, 0.4%, and 1.0%. Findings indicate that at the concentration of 1.0% magnesium stearate, the compressed lozenge exhibited uniform appearance without any white edges, meeting the organoleptic properties as outlined in Table 5.

Table 5: ***Survey of magnesium stearate in lozenge formulations.***

Percentage of glidants	0.1%	0.5%	1.0%
Appearance/ Description	 With white edges	 With white edges	 Without white edges

The investigation into flavoring agents aimed to determine their type, proportion, and optimal combination. It was notible that combining 0.2% peppermint essential oil or dissolving 0.1% menthol in ethanol during the final mixing stage failed to impart a sufficient cooling sensation. Conversely, uniformly mixing 0.1% menthol during the final mixing stage yielded superior results with simpler operations and lower concentrations of flavoring agents.

Furthermore, taste testing of compressed lozenges was conducted using various excipients such as sodium saccharin, acesulfame K, and aspartame at a ratio of 0.05%. The lozenges exhibited the most pleasant sweet taste without a bitter aftertaste when utilizing sodium saccharin as the sweetener. Additionally, combining sodium saccharin during the final mixing stage resulted in a favorable mouthfeel and without white edges on the compressed lozenge.

Figure 1: ***The cough lozenge surface.***

The study successfully prepared compressed lozenges using the Vietnamese traditional remedy "Bai Bu Bu Fei Tang". The finalized formulation is detailed in Table 6.

Table 6: ***The composition of the finalized lozenge formulation.***

Component	Weighing (mg)
Soft extracts (15.0% moisture content)	200.0
Lactose monohydrate	200.0
Mannitol	583.5
Povidon K30	005.0
Magnesi stearate	010.0
Menthol	001.0
Sodium saccharin	000.5

3.4. Evaluation of lozenges

The evaluation results revealed that the tablets exhibited a pleasant mouthfeel, devoiding of any abrasiveness, and offered a sweet, refreshing taste. With an average weight of 0.999 g, the lozenges had an average disintegration time of 42.5 minutes (Table 7).

Table 7: ***Quality control tests of lozenges***

Specification	Results
Appearance/ Description	- The lozenges exhibit a rounded shape with smooth surfaces, intact edges, uniform shine, and absence of breakage. - The lozenges possess a distinct medicinal aroma and impart a refreshing, sweet taste sensation.
Thickness	4.07 ± 0.05
Disintegration	42.5 min
Uniformity of weight	Pass
Friability	0%
Identification	Pass

Furthermore, the identification tests for *Radix Stemonae*, *Fructus Terminaliae chebulae*, and menthol presented in the compressed lozenges exhibit positive outcomes, aligning with the corresponding standard solutions of *Radix Stemonae*, *Fructus Terminaliae chebulae*, and menthol (Figure S2).

3.5. Antimicrobial activity

The *in vitro* antimicrobial assessment revealed that both the concentrated extract and the obtained lozenges at the same concentration (100 mg/mL) exhibited an effective antimicrobial activity against MSSA strain, as reflected by an antibacterial diameter of 1.5 cm and 3.2 cm, respectively (Figure 2). The comparison between the obtained lozenges and the concentrated extracts reveals that lozenges exhibit superior antibacterial activity. This disparity suggests that the presence of menthol in the lozenge formulation may contribute to its heightened antibacterial efficacy.

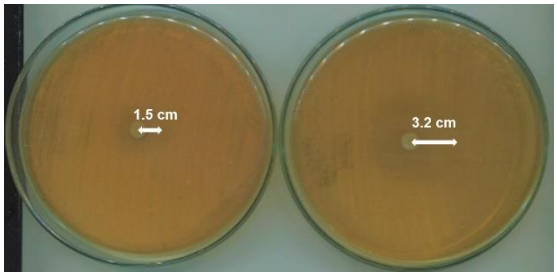

Figure 2: ***Results of in vitro antimicrobial activity testing***.
(Left: the concentrated extract; Right: the compressed lozenge).

IV. CONCLUSION

Diluents including lactose monohydrate and mannitol were critical for the wet granulation process of this lozenge type. However, high concentration of lactose (lactose:extract ratio above 1:4 (w/w)) exhibited elevated moisture absorption and induced poor flowability. On the contrary, granules with high concetration of mannitol (mannitol:extract ratio above 1:4.5) showed improved flowability but higher moisure uptake. Therefore, a combination of these two diluents at an extract:lactose:mannitol ratio (1:1:3) was used and resulted in granules with favorable flowability and reduced moisture absorption [16-17]. The use of PVP K30 in relatively low concentration (0.5%) produced granules with acceptable flowability. This outcome might be attributed to the presence of sugars and mucilage content in the herbal extract. Furthermore, the usage of sodium saccharin (0.05%) and menthol (0.1%) not only preserved the lozenge quality but also enhanced its palatability. Unexpectedly, the obtained lozenge not only complied with the quality standards outlined in the Vietnamese Pharmacopoeia V but also exhibited a better antimicrobial activity compared to the concentrated extract at the same concentration of dry extract. This better antimicrobial activity could be explained by the presence of menthol.

The study was the first study in Vietnam that successfully developed a modern dosage form for the Vietnamese traditional remedy "Bai Bu Bu Fei Tang", enabling its commercialization in the Vietnam pharmaceutical market for chronic cough treatment.

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