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Original Article

DEVELOPMENT OF A TABLET FORM OF LIU WEI DI HUANG EXTRACT

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ABSTRACT

Objective: Develop an effective and stable tablet form of Liu Wei Di Huang (LWDH).

Methods: LWDH extract was obtained by decoction (TC) and reflux with water (WR). Extracts were concentrated and analyzed by HPLC-PDA using loganin as the bioactive marker. Adsorbents, tablet strength and friability, and tablet quality and stability were evaluated.

Results: Extraction of LWDH formula from raw materials using WR yielded higher concentrations of loganin than TC. The best formulation of LWDH tablets included Avicel®PH101, corn starch, purified talcum, magnesium stearate and Cab-osil® with about 97.40 % of the label amount of active marker. Excluding moisture from the product reduced marker degradation, suggesting a product shelf life 12+months. Finished tablets were uniform in weight, friability, disintegrated in<30 min, had good microbial and heavy metal contamination safety profiles and was stable.

Conclusion: Extraction of LWDH formula using reflux with water produces higher yields than decoction. A suitable tablet formulation consists of dried water extract (38.83 %), corn starch (29.13 %), Avicel®PH101 (29.13 %), purified talcum (0.97 %), magnesium stearate (0.97 %) and Cab-osil® (0.97 %) prepared by wet granulation. Excluding moisture from the product reduces product degradation, suggesting a shelf life of 12+months. LWDH tablets avoid traditional formulation problems (high dosages, unacceptable taste and odor, lack of product uniformity, contamination with microorganisms and heavy metals), and are a good alternative for patients and TCM practitioners.

Keywords: Liu Wei Di Huang, Chinese Traditional medicine, Tablets, Quality, Stability.

INTRODUCTION

Traditional Chinese medicine (TCM) is a popular form of alternative medicine which provides supplements as well as treatments for some chronic diseases or conditions. Treatments are based on the relationship of yin and yang (阴阳), five phases (五行) and Qi (氣) [1].

Most TCM textbooks and TCM teachers mention that kidney deficiency in women relates to a menopause disorder [2]. Liu Wei Di Huang (六味地黄/lWDH) is one of the TCM herbal formulas used in the treatment of menopause problems caused by kidney yin deficiency [3-4]. The LWDH formula consists of six kinds of crude drugs: Shudihuang (熟地黄) from *Rehmannia gultinosa*, Shanshuyu (山茱萸) from *Cornus officinalis*, Shanyao (山药) from *Dioscorea Opposite*, Zexie (泽泻) from *Arisma orientale*, Fuling (茯苓) from *Wolfiporia extensa* and Danpi (丹皮) from *Paeonia suffruticoas* [3-6] (fig. 1). The Pharmacopoeia of the People's Republic of China (2005) describes two traditional dosage forms: Liu Wei Di Huang Wan (六味地黄丸) which is a pill form (Wan 丸 = pills) and Liu Wei Di Huang Keli (六味地黄顆粒) which is a granulate form (Keli 顆粒 = granules). The dosages are 27 g/day for pills or 15 g/day for granules, taken in three equal doses of 9 g and 5 g, respectively. The loganin content in both forms should not be lower than 4.5 mg/dose [5]. In addition to pills and granules, LWDH formula can be prepared as a solution obtained by decoction [3, 6].

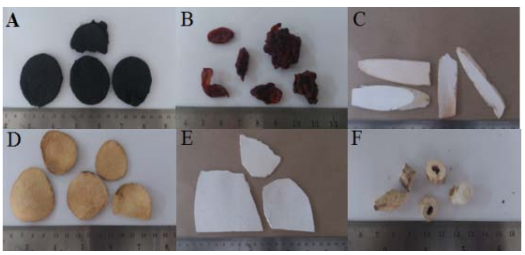

Fig. 1: Crude drugs in the liu wei di huang formula: Shudihuang (A), Shanzhuyu (B), Shanyao (C), Zexia (D), Fuling (E) and Danpi (F)

The traditional dosage forms have disadvantages such as being inconvenient to use, having an unacceptable taste or odor, and having variations of content uniformity as well as contamination with microorganisms and heavy metals [7-8]. This study attempted to develop an LWDH formula in tablet dosage form which avoids those disadvantages.

MATERIALS AND METHODS

Materials

Raw materials used in preparing the Liu Wei Di Huang formula were purchased from the Vejpong Pharmacy Co., ~~Ltd~~. (Thailand). Avicel® PH101 was purchased from DMV-Fonterra Excipients GmbH & Co. KG (Germany). Corn starch was purchased from CM Chemical & Lab Supply (Thailand). Cab-osil® was purchased from Sigma-Aldrich (Germany). Magnesium stearate was purchased from Riedel-de Haen (Germany). Purified talcum was purchased from Ilshin Industrial Co., Ltd. (China). Loganin CRS, 5-(hydroxymethyl)-furfural CRS, ursolic acid CRS and paeonol CRS were purchased from Fluka (Germany). Acetonitrile HPLC grade, ethanol HPLC grade, phosphoric acid AR grade and 95 % ethanol AR grade were purchased from RCI Labscan (Thailand).

Apparatus

Chromatographic analysis was carried out using an HPLC system (Shimadzu, Japan) with degasser (DGU-20A5), pump (LC-20AD), autosampler (SIL-20AC), column oven (CTO-20A), diode array detector (SPD-M20A) and communication bus module (CBM-20A). Columns used in this study were Inertsil ODS-3 C18 reversed phase columns. Chromatograms were analyzed using LC Solutions software.

Evaluation of the quality of the crude drugs

Raw materials, the crude drugs used in producing the LWDH formula, were evaluated in the areas of physical characteristics, chemical identification, water content, total ash, acid-insoluble ash, extractive value and chemical content following the Chinese Pharmacopoeia (2005) [5].

Extraction of liu wei di huang

The crude drugs Shudihuang, Shanzhuyu, Shanyao, Zexie, Fuling and Danpi were measured in proportions of 24:12:12:9:9:9 to make up a total weight of 75.0 g, then they were mixed together. The LWDH formula was extracted using two different methods: decoction imitating traditional procedures and reflux with water. The water extracts obtained by each of the two extraction methods were concentrated separately by rotary evaporator.

Dose calculation of liu wei di huang water extract

Standard preparation [5]

Loganin CRS a form of iridoid glycoside (fig. 2), was prepared in 50 % ethanol at a concentration of 0.224 mg/ml. The solution was filtered through a 0.45 micron nylon membrane filter then injected into an HPLC-PDA by an autosampler with a 10 µl loop.

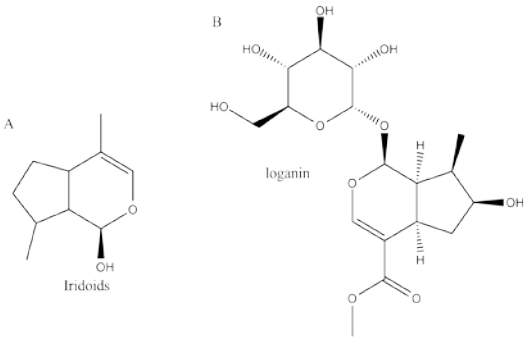

Fig. 2: Chemical structure of iridoids (A) and loganin (B)

Sample preparation

The water extracts obtained from decoction (TC) (1.5100 g) and reflux with water (WR) (1.0000 g) were dissolved in 40 ml of 50 % ethanol, weighed, sonicated for 30 min, allowed to cool and then weighed again for impletion of evaporated solvent. The sample solutions were filtered using Whatman No.1 filter paper. The samples, 5 ml of filtrate made up to 10 ml in a volumetric flask, were filtered using a 0.45 micron nylon membrane filter and then injected in volumes of 100 □l to HPLC-PDA by an autosampler [5, 9].

Chromatographic analysis system

The chromatographic system used was modified from the methods of Xie *et al.* [9] and the Pharmacopoeia of the People's Republic of China (2005) [5]. The stationary phase used C18 reversed phase silica gel and the mobile phase used a mixture of acetonitrile (line A) and 0.015 % phosphoric acid (line B). The flow system was a gradient system: 0-3 min–(start) isocratic line A = 5 %; 3-30 min–gradient line A to 60 %; 30-33 min–gradient line A to 70 %; 33-49 min–isocratic line A = 70 %; 49-50 min–gradient line A to 5 %; 50-60 min (stop)–isocratic line A = 5 %. Flow rate of the system was 1 ml/min. The column was temperature controlled at 35 °C and the detection wavelength was 236 nm. Three replications were carried out for each sample of LWDH water extract.

Calculation of drug dosing from LWDH extract

The approximate dosage (AD) of Liu Wei Di Huang extract, measured to equal the dose of traditional dosage forms, was calculated by comparing loganin content. The water extract with the higher loganin content per gram of extract, i.e., the lower dose, was selected to be an active ingredient in the development of the LWDH tablets.

Development of tablets from LWDH extract

Adsorbent selection

LWDH extract was divided into three batches of 500–600 mg each and put into three mortars. Three different types of adsorbent, corn starch, lactose and Avicel® PH101, all commonly used in the manufacture of Chinese herbal medicines [10], were put on individual watch glasses. The combined weight of the watch glass plus adsorbent was recorded (weight A). The adsorbents were evaluated for their adsorptibility by adding quantities of each type into one of the mortars and slowly mixing that with the extract until the extract powder appeared clearly. The watch glass and the remaining adsorbent were weighed (weight B). The quantity of each type of adsorbent used for powder reformation was calculated as the difference between weight A and weight B. Adsorbents with an adsorption ratio of not more than 1:2 were selected as the excipients for development of tablet formulation.

Development of tablet formulation

LWDH extract was weighed and mixed with the adsorbents to obtain a wet mass appearance with the geometric dilution technique using a mortar and pestle. The wet mass was passed through a No. 8 sieve to obtain wet granules [11] which were dried in a hot air oven at 50 °C (below the 65 °C swelling temperature of corn starch [12]) until loss on drying was not more than 5 % (in the case of Avicel®, not more than 7 % [12]) to achieve appropriate tablet compressibility [11]. The granules were passed through a No. 12 sieve using an oscillating granulator [11, 13] to obtain dry granules. Purified talcum, magnesium stearate and Cab-osil®, each weighing 1 % of the weight of the finished granules, was then mixed with the finished granules by tumbling for 1 min. The mixture was compressed by a single stroke tablet machine to create the finished tablets. The tablets were then evaluated for friability and disintegration time to evaluate the effect of adsorbents on those parameters. Adjustments to the tablet formulation were made based on the evaluation results.

Evaluation tablet quality

The tablets with a suitable formulation were evaluated for quality based on physical appearance, weight variation, friability, hardness, disintegration time, loganin (marker) content, plus microbial and heavy metal contamination, quality parameters provided by the Thai FDA guidelines for finished herbal products [14].

Stability evaluation of tablets from LWDH extract

Tablets were packaged in two types of container: either in glass bottles with light protection (container B) or in laminated, heat sealed packages which were then inserted into glass bottles with light protection (container L). Containers were kept in a stability chamber either at the standard conditions of 30 °C and 65 % relative humidity (RH) or at accelerated conditions of 40 °C and 75 % RH. Samples were evaluated for appearance, hardness, friability, disintegration time and loganin content on day 0 and then again at day 30 and day 90.

RESULTS AND DISCUSSION

Raw materials used in preparation of the LWDH formula were purchased from herbal drug stores in Thailand; quality was evaluated following the Chinese Herbal Pharmacopoeia (2005) [5]. Macroscopic and microscopic characteristics of all crude drugs were in accordance with the herbal monograph in that document. The chemical identification of Shudihuang, Shanzhuyu and Danpi was made with the Thin Layer Chromatographic (TLC) technique using 5-(hydroxymethyl)-furfural, ursolic acid and paeonol as chemical markers (see chemical structures in fig. 3). TLC chromatograms of three of the herbal medicines showed that all samples contained the specified chemical components as described in the herbal monograph (fig. 4). 5-(hydroxymethyl)-Furfural (Retard factor (Rf) = 0.6) was found in Shudihuang, Shanzhuyu contained Ursolic acid (Rf = 0.6), and paeonol (Rf = 0.7) was found in Danpi. All crude drugs in the LWDH formula were identified by macroscopic and microscopic inspection and confirmed by chemical identification. Parameters evaluated for all the crude drugs included water content, total ash, acid-insoluble ash, extractive value and chemical content [5]. The results (table 1) show that all the samples were of standard quality as specified in the Chinese Herbal Pharmacopoeia (2005) [5].

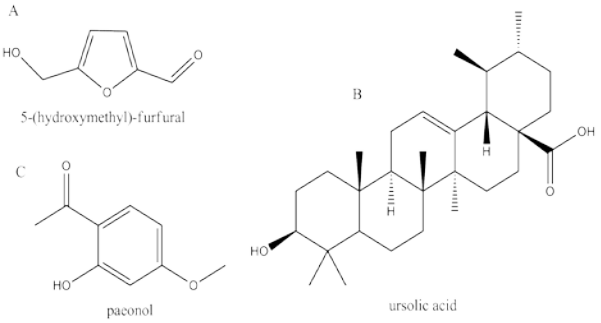

Fig. 3: Chemical structure of 5-(hydroxymethyl)-furfural (A), ursolic acid (B) and paeonol (C)

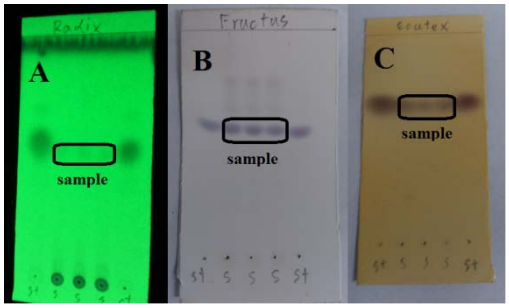

Fig. 4: TLC chromatograms of Shudihuang (A), Shanzhuyu (B) and Danpi (C)

The LWDH formula extracted by the reflux method gave higher yields than decoction (65 % vs 55 % by weight). Water extracts obtained from the two different methods were analyzed for chemical content by HPLC-PDA with loganin used as the chemical marker [5, 9]. Loganin was appeared in HPLC chromatograms at retention time of 16.8 min (fig. 5). Because loganin was specified as the chemical marker in the LWDH formula with a percentage label amount per dose, loganin content can be used to calculate drug dosing from LWDH water extracts. Using the HPLC chromatograms, loganin content of LWDH water extracts was calculated by area under curve (AUC) comparison (table 2). It was found that the WR extract contained a higher loganin content per gram of extract than the TC extract. For that reason, WR extract was selected to be an active ingredient in the development of LWDH tablets.

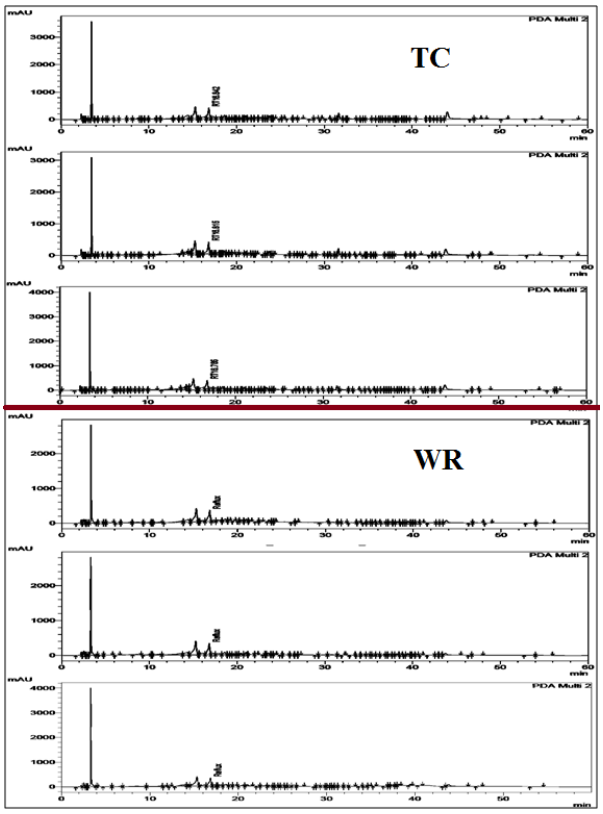

Fig. 5: HPLC chromatograms of TC and WR

Table 1: Quality of crude drugs used

Plant name	Parameter				
	Water Content (%)	Total Ash (%)	Acid-insoluble Ash (%)	Extractive Value (%)	Marker Content (%)**
Shudihuang	n/a	5.55 (≤6.0)*	1.91 (≤2.0)*	69.37 (≥60.0)*	n/a
Shanzhuyu	7.99 (≤16.0)*	4.90 (≤6.0)*	0.42 (≤0.5)*	55.07 (≥50.0)*	0.74 (≥0.6)*
Shanyao	n/a	n/a	n/a	n/a	n/a
Zexie	n/a	2.71 (≤5.0)*	0.13 (≤0.5)*	n/a	n/a
Fuling	6.77 (≤15.0)*	0.25 (≤4.0)*	0.03 (≤2.0)*	n/a	n/a
Danpi	6.75 (≤13.0)*	3.59 (≤5.0)*	0.28 (≤1.0)*	15.63 (≥15.0)*	1.33 (≥1.2)*

n/a = Data not provided in the monograph, *The upper limit or lower limit of crude drugs as specified in the monograph, **Standard markers: loganin for Shanzhuyu and paeonol for Danpi

Table 2: Loganin content found in LWDH water extract

Sample concentration	AUC	Average	RSD	LC (mg/g)	AD (g)
Loganin 0.224 mg/ml	2 675 093	2 677 256	0.07	-	-
	2 678 431				
	2 678 245				
TC 18.875 mg/ml	5 580 558	5 515 420	2.30	2.44	2.0
	5 369 509				
	5 596 193				
WR 12.500 mg/ml	5 014 786	5 109 692	1.71	3.42	1.5
	5 186 468				
	5 127 821				

RSD = Relative Standard Deviation

Three types of adsorbents were selected for evaluation: lactose for its water solubility and corn starch and Avicel® PH101 for their adsorptibility [12, 15-16] as well as their common usage in Chinese herbal manufacturing [10]. The adsorbents were evaluated for their suitability as excipients for the LWDH tablet formula by their ability to change the semi-solid extract into a powder. The least desirable adsorbent was lactose because of its higher ratio of extract to adsorbent (table 3). It has also been reported that lactose is incompatible with loganin due to glycosidic interaction between lactose and glucose in loganin [10]. Thus, only corn starch and Avicel® PH101 were found to be suitable excipients in LWDH extract tablet formulation.

Table 3: Quantity of adsorbent needed to convert semi-solid extract to powder

Adsorbent	Weight of WR extract (mg)	Quantity of adsorbent (mg)	Ratio of WR extract to adsorbent
Lactose	635	2785	1:4
Corn starch	505	1000	1:2
Avicel® PH101	590	515	1:1

Tablets must be sufficiently rugged to withstand some level of physical stress from handling, but they must also disintegrate within the required time to allow them to dissolve and be absorbed into body (<30 min for herbal tablets) [14-15, 17]. Two tablet formulations of LWDH extract, F1 and F2, were prepared for preliminary studies of friability and disintegration time (table 4). As shown in table 5, F1 tablets showed poor ruggedness in the friability test (10.49 % with 8 cracked tablets) but had a good disintegration profile (9.53±0.72 min). In contrast, F2 tablets had a very good friability profile (0.23 % with no broken tablets) but a poor disintegration test profile (>30 min). The propensity of corn starch to swell in water promoted disintegration of F1 tablets, but, with the exception of starch paste, it is not a good binder in tablets [12], resulting in the low friability profile of the F1 tablets. In the F2 tablets, the excipient Avicel® PH101 had good properties both as a binder and as a disintegrant; however, in higher concentrations in tablets (20-90 %), its binding properties overwhelm the disintegrant properties which appear at lower concentrations (5-15 %). Based on the friability and disintegration time of the F1 and F2 tablets, a modified formulation was developed which included both adsorbents (table 6).

Table 4: Initial formulations (F1 and F2) used in determining friability and disintegration time profiles

Component	Formulation (mg/tablet)	
	F1	F2
WR extract	500	500
Avicel® PH101	-	500
Corn starch	1000	-
Purified Talcum	15.0	10.0
Mg stearate	15.0	10.0
Cab-osil®	15.0	10.0

Table 5: Friability and disintegration time profiles of F1 and F2 tablet formulations of LWDH extract

	Friability			Disintegration	
	Weight of 20 tablets (g)		%FR	Time (min)	Avg. (min)
	Before	After			
F1	31.6848	28.3612	10.49*	10.00 10.17 9.00 10.33 9.00 8.67	9.53±0.72
F2	21.1620	21.1138	0.23 **	31.17 32.00 30.33 34.50 29.00 35.00	32.00±2.35

% FR = % friability; Avg. = Average, *8 tablets cracked, **No tablets broke

Table 6: Composition of the modified tablet formulation of LWDH extract developed based on friability and disintegration profile tests of the F1 and F2 formulations

Component	Quantity (mg/tablet)	Role
WR extract	500	Active ingredient
Avicel® PH101	375	Adsorbent/Binder
Corn starch	375	Adsorbent/Disintegrant
Purified Talcum	12.5	Anti-adherent
Mg stearate	12.5	Lubricant
Cab-osil®	12.5	Glidant

The finished tablets, oval, 23.2 x 10.3 x 6.7 mm thick, brownish-white in color and tasteless, were evaluated following Thai FDA guidelines for finished herbal products [14]. They were found to meet the quality control specifications of those guidelines. Weight variation, tablet friability, disintegration time, tablet hardness, and assays for loganin content are shown in Tables 7-11; details of microbial and heavy metal contamination are shown in table 12.

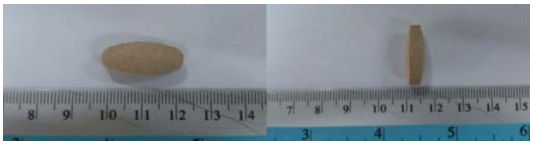

Fig. 6: Finished tablets were plain, oval, 23.2 x 10.3 x 6.7 mm thick, brownish-white in color, odorless and tasteless

Table 7: Weight variation of finished tablets

Tablet	Weight (g)	Tablet	Weight (g)
1	1.3061	11	1.3266
2	1.3293	12	1.3062
3	1.3160	13	1.3163
4	1.3229	14	1.3056
5	1.3261	15	1.3263
6	1.3118	16	1.3069
7	1.3257	17	1.3139
8	1.3136	18	1.3174
9	1.3286	19	1.3164
10	1.3105	20	1.3118
Average±SD 1.3169±0.008 g			
Variation±0.61 %			

Table 8: Friability profile of finished tablets

	Weight of 20 tablets (g)		% Friability	Amount of tablet breakage
	Before	After		
Test 1	26.3666	26.3600	0.025	0 tablets
Test 2	26.3689	26.3635	0.020	0 tablets
Test 3	26.3750	26.3690	0.023	0 tablets
Average friability±SD 0.023±0.003 %				

Table 9: Disintegration profile of finished tablets

Tablet	Disintegration time (min)	Tablet	Disintegration time (min)
1	23.33	4	25.00
2	24.17	5	24.66
3	23.50	6	23.33
Average±SD (min)	24.25±0.70		

Table 10: Hardness of finished tablets

Tablet	Hardness (kg)	Tablet	Hardness (kg)
1	11.0	6	11.0
2	11.0	7	11.0
3	12.0	8	11.0
4	11.5	9	11.5
5	11.0	10	11.0
Average hardness±SD 11.20±0.35 kg			

Table 11: HPLC analysis of marker content in finished tablets

Sample/Standard details					
Sample	Weight of 10 tablets= 12.5549 g Average weight of 1 tablet= 1.25546 g Injection volume = 100 □l				
Standard (loganin)	Concentration= 0.224 mg/ml Injection volume = 10 □l				
HPLC marker content					
	Injection No.	AUC	Average	RSD	Loganin Content (mg/tab)
Loganin	1	2 668 874	2 667 850	0.05	n/a
	2	2 666 250			
	3	2 668 453			
Sample	1	2 510 331	2 474 236	1.32	1.66
	2	2 465 971			
	3	2 446 407			
Desired loganin content in 1 tablet (mg)					1.71
Actual % of label amount of loganin					97.40 %

Note: LC = Loganin content; n/a = not applicable

Stability evaluation of the finished tablets was conducted using two different types of containers, glass bottles with light protection (container B) and laminated, heat sealed packages inserted into glass bottles with light protection (container L), under standard conditions (30 °C/65 % RH) and under accelerated conditions (40 °C/75 % RH) over a period of 90 days. Tablets in each of the container types showed good physical stability under both conditions (table 13). In terms of chemical stability, tablets in container B showed a degradation of the active marker (loganin) of more than 10 % after 30 days under accelerated conditions of 40

°C/75 % RH; degradation of loganin content of tablets in container L after 90 days was still less than 10 % under both conditions (table 13 and fig. 7). These results indicate that moisture can affect loganin degradation, so exclusion of moisture from containers is important for minimizing degradation of quality. The laminated heat sealed packs in a glass bottle (container L) provided better moisture protection than the glass bottles alone (container B). Product shelf life in container L could be expected to exceed 12 months; however, long term stability testing is required to confirm potential shelf life [18].

Table 12: Quality evaluation of the LWDH finished tablets

Parameter	Guidelines and/or criteria	Results
Appearance	Shape, color, odor and/or taste of the product	See fig. 6
Weight Variation	±15 % from the average weight	±0.61 % from the average weight
Friability	Friability not more than 1 %; no detectable capping or laminating of tablets	0.023±0.003 %; no capping or laminating detected
Hardness	n/a	11.20±0.35 kg
Disintegration Time	Not more than 30 min	24.25±0.70 min
Loganin content	90-110 % of label amount	97.40 % of label amount
Microbial contamination*	- Aerobic bacteria ≤ 5.0 x 10^3/g - Enterobacteria ≤ 5.0 x 10^3/g - Yeast/Fungi ≤ 5.0 x 10^3CFU/g - *Escherichia coli* ≤ 5.0 x 10/g - No detection of *Staphylococcus aureus* in 1 g - No detection of *Clostridium* spp. in 10 g - No detection of *Salmonella* spp. in 10 g	- Total aerobic bacteria = 3.5 x 10^2 CFU/g - Enterobacteria<10/g - Total Yeast/Fungi<10 CFU/g - *E. coli* = Not detected in 10 g - *S. aureus* = Not detected in 1 g - *Clostridium* spp. = Not detected in 10 g - *Salmonella* spp. = Not detected in 10 g
Contamination of heavy metal*	- Arsenic ≤ 4 ppm - Cadmium ≤ 0.3 ppm - Lead ≤ 10 ppm	- Arsenic = 0.1 ppm - Cadmium = Not detected - Lead = Not detected

n/a = No guidelines provided in the monograph, *Testing conducted by Regional Medical Science Center 10 (Chiang Mai).

Table 13: Stability evaluation of tablets for LWDH extract

Container	Condition	Appearance	FRI (%)	HAR (kg)	DIS (min)	LOG (mg/tab)
Day 0						
Both containers	30°C/65 % RH 40°C/ 75 % RH	See fig. 6	0.023±0.003	11.20±0.35	24.25±0.70	1.66
Day 30						
Container B	30°C/ 65 % RH	no significant change	0.013±0.006	11.25±0.43	23.83±1.56	1.65
	40°C/ 75 % RH	no significant change	0.005±0.002	11.10±0.39	23.70±1.09	1.20
Container L	30°C/ 65 % RH	no significant change	0.014±0.017	11.10±0.39	24.36±0.94	1.59
	40°C/ 75 % RH	no significant change	0.019±0.023	11.25±0.43	24.22±0.90	1.62
Day 90						
Container B	30 °C/65 % RH	no significant change	0.007±0.004	11.10±0.32	23.42±0.95	1.57
	40°C/75 % RH	no significant change	0.011±0.006	11.05±0.37	24.44±0.83	1.24
Container L	30 °C/65 % RH	no significant change	0.010±0.006	11.15±0.41	23.64±1.10	1.60
	40°C/75 % RH	no significant change	0.009±0.006	11.15±0.47	23.97±0.93	1.57

Note: FRI = Friability; HAR = Hardness; DIS = Disintegration time; LOG = Loganin content

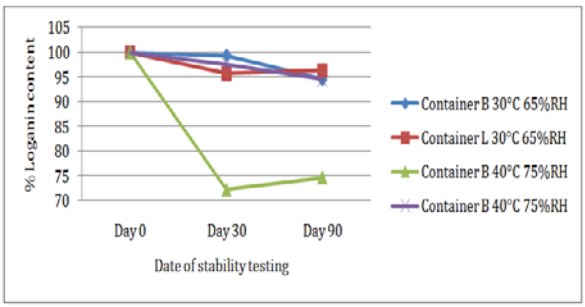

Fig. 7: Stability of Loganin content in LWDH tablets packed in two different types of containers (B = glass bottle, L = laminated, heat sealed package inside a glass bottle) and stored under two different conditions for a period of 90 days (lower limit = 90 %)

CONCLUSION

Extraction of standard quality LWDH formula raw materials using the reflux with water (WR) produces higher yields than decoction (TC). WR extract also contains higher loganin content per gram of extract than TC extract, making it the preferred method for LWDH tablet formulation. A suitable tablet formulation consists of dried water extract (38.83 %), corn starch (29.13 %), Avicel®PH101 (29.13 %), purified talcum (0.97 %), magnesium stearate (0.97 %) and Cab-osil® (0.97 %) prepared by wet granulation. Exclusion of moisture can significantly reduce degradation of the products' chemical marker, suggesting an extrapolated product shelf life of more than 12 months. In addition, LWDH tablets avoid problems of traditional formulations including high dosages, unacceptable taste and odor, lack of product uniformity as well as potential contamination with microorganisms and heavy metals, making tablets a good alternative for both patients and TCM practitioners.

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CONFLICT OF INTERESTS

Declared None

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