Formulation of *Houttuynia cordata* Standardized Extract Tablets

Orachorn Sriya[1], Isada Sirimontree[2], Siriporn Panthuvanich[2] and Nisit Kittipongpatana[1],*

[1]Department of Pharmaceutical Sciences, Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200, Thailand
[2]Defence Pharmaceutical Factory, Defence Industry and Energy Center, Office of Permanent Secretary of Defence, Bangkok 10110, Thailand

**Corresponding author: E-mail: nisitk@pharmacy.cmu.ac.th*

ABSTRACT

The preparation and quality control of standardized Houttuynia cordata (HC) extract, and the formulation of tablets containing HC extract (HCE) as a food supplement product were studied. HCE was obtained by repeated maceration of dry HC powder (HCP) with ethanol and solvent removal under reduced pressure. Standardization of HCE was carried out using chromatographic methods. HCE was adsorbed onto corn starch or silicified microcrystalline cellulose 90 (SMCC90) to obtain HCE powder (HCEP), which was formulated into tablets. Quality control (QC) of HCEP and tablets was performed after preparation and after stability tests for 3 months at room temperature (RT) and at 45˚C. The yield of HCE was 5.85% dried weight (DW). Chromatographic analyses showed quercetin and rutin as major components and potential QC markers. Appearances and moisture analyses of HCEP indicated SMCC90 as the superior adsorbent. The optimum formulations, with 5.29 and 3.30% Loss on drying (LOD), and repose angles of 46.2±4.8˚ and 28.1±2.6˚ for HCEP and bulk, respectively, were selected. Weight of tablets was 250±18.75 mg while hardness, friability and disintegration time were 41.5±3.2 N, 0.04% and 1.23 min, respectively. Stability test revealed that moistures of HCEP and bulks kept at RT were lower than those stored at 45˚C. Tablet hardness decreased after storage at 45˚C. All tablets passed friability tests, while the disintegration times were between 1-2 min. These results suggested that standardized HCE can be employed in the formulation of food supplement tablets with good uniformity and stability.

Key words: *Houttuynia cordata,* Standardized extract, Chromatography, Food supplement, Tablet formulation

INTRODUCTION

Houttuynia cordata Thunb. (Saururaceae) (HC) is an important traditional medicine of East and South East Asia, especially China, Japan and Thailand, where the plant is known as Kao-Tong or Plu-Kao (Bansiddhi et al., 2003). HC was reported to contain several groups of phytochemicals. Among these, flavonoids – a group of phenolic compounds that occur in both glycosidic and aglycone forms – are of importance as they are found to possess many pharmacological properties (Matsui et al., 2005; Formica and Regelson, 1995). Major flavonoids of HC were rutin and quercetin (Havsteen, 2002). Rutin was reported to treat and prevent severe acute respiratory syndrome (SARS) (Zhang and Chen, 2008) while quercetin was found to inhibit tumor growth via blockage of protein kinase activity and lactate transport (Formica and Regelson, 1995).

Literature reviews on pharmaceutical preparation of HC revealed the use of this herb in many types of products, including as food supplement, drug, beverage and cosmetics. HC was prepared in the form of injection (Lau et al., 2008; Lu et al., 2006). HC was also combined with other herbal plants in capsule dosage form (Li, 2003) and injection (Yu, 2007). Extracts of HC and other medicinal plants were prepared as buccal tablet for acute and chronic pharyngitis and stomatitis (Xuan and Lui, 2004). In Thailand, the Government Pharmaceutical Organization (GPO) manufactures a capsule formulation containing HC and other plant extracts for use as food supplement to improve immune response (Sriwanthana et al., 2007). Preparations of sole HC are commercialized in the forms of powdered plant capsule, fermented drinks and wines. The form of tablet, both of HCP or HCE, has not been found.

Tablet is generally the most desirable dosage form as it has advantages over other forms in terms of consistency and accuracy of active compound(s) for a unit dose, tampered-proof, low cost, convenience of taking and carrying and storage. However, several reports suggested that rheological property and compressibility were two main obstacles for tabletting of plant extract. Proposed solutions to overcome these problems included the wet granulation, the preparation of spray-dried extract powder, or the use of pharmaceutical excipients to enable direct compression (Plazier-Vercamen and Bruwier, 1986; Díaz et al., 1996; Renoux et al., 1996; Palma et al., 2002). Tablets of plant extract contained higher amounts of active components than those in capsules of herbal powder. In addition, herbal extract formulation minimized the rate of microbial contamination often associated with the herbal powder preparation. The quality control of active compounds can also be facilitated in the extract formulation which leads to the higher quality and safety of medicinal plant products for modern medicines. This study reports the preparation and quality control of standardized HCE and the formulation of stable tablets containing consistent HCE as a food supplement product.

MATERIALS AND METHODS

Materials

All chemicals used in the preparation and analysis of HCE were of analytical grade or equivalent, except those used in high performance liquid chromatography (HPLC) were of HPLC grade. Standard rutin and quercetin were purchased from Fluka, Germany. SMCC90 was from JRS Pharma LP., Germany (batch no. P9D7D55). Corn starch was the product of Roquette, France (lot no. 3959 0094). Other pharmaceutical excipients were of pharmaceutical grade. GPO's NaturePlex® capsules were purchased from a local pharmacy store.

Preparation of HC plant materials

Fresh aerial parts of 3-month grown HC, from which the leaves, branches and posy were reportedly contained flavonoid-glycosides (Eui et al., 1996; Bansiddhi et al., 2003), were obtained from Sun-Phi-Sua sub-district, San-Sai district, Chiang Mai in August-October 2008. The identity of the plant was authenticated and a herbarium voucher specimen was prepared and deposited at the Faculty of Pharmacy, Chiang Mai University. Plant materials were dried at 50˚C for 3 days in a hot air oven. Dried HC was milled with cutting mill and was sieved through mesh no.40 to obtain HCP. The moisture content (%LOD) of the dried powder was determined.

Extraction of HCP

HCP was macerated with ethanol (Kim et al., 2007) at a ratio of HCP: 95% ethanol as 1:10 for 20 h (3 times), then filtered through the filter paper (Whatman no.1). The filtrate was collected, combined and evaporated under vacuum at 50˚C via a rotary evaporator to obtain HC extract (HCE) (Zhang and Chen, 2008). HCE was weighed to calculate yield percentage, the weight of tablet and the concentration for quality control.

Preparation of HCE for analysis

HCE was fractionated with liquid-liquid partition technique into four portions: hexane (F1), chloroform (F2), ethyl acetate (F3) and water (F4). Each fraction was evaporated to dryness and reconstituted in methanol.

Identification of Terpenes and Flavonoids in HCE

HCE and F1-F4 were analyzed using thin-layer chromatography (TLC) with rutin and quercetin as standards. The evaluation was carried out under visible light (VL) and ultraviolet light (UV) at 254 and 365 nm. Silica gel GF_{254} Aluminum sheets and mixed solvents were used as stationary phase and mobile phase, respectively, with 15 cm solvent front Geraniol (0.2%v/v in methanol) was used as a standard in terpene test, with petroleum ether: ethyl acetate: formic acid ratio of 47:2:1 as developing solvent (DVS). Vanillin-phosphoric acid was used as spraying reagent and the sheets were heated at 120˚C for 10 min before the chromatograms was observed. For flavonoid tests, rutin and quercetin were used as standards. DVS was the upper fraction of diethyl ether: formic

acid: water (90:20:30) mixture (Wagner et al., 1990; Bansiddhi et al., 2003). The chromatogram was observed after 1% aluminum chloride in ethanol was sprayed and allowed to dry at RT.

Formulation and compaction of HCE tablets

Preparations of HCEP

Adsorption of HCE was tested on two adsorbents: corn starch (Sandhu and Singh, 2007) and SMCC90 (Tobyn et al., 1998), to obtain suitable powder for direct compression. HCE and adsorbents were mixed at the ratio according to Table 1 in a mortar. Each mixture was dried at 50˚C for 20 h, then evaluated and selected.

Table 1. Ratio of HCE and adsorbents

Formulation	Ratio of HCE: Adsorbent	
	Corn starch	SMCC 90
1	1:24	-
2	1:12	-
3	1:8	-
4	1:4	-
5	1:1	-
6	-	1:2
7	-	1:3

Formulation of HCE tablets

HCEP (80%) was mixed with a number of pharmaceutical excipients at various combinations (Table 2). Each formulation was subjected to tabletting via a hydraulic press. Tablets were then evaluated according to standard methods described in Pharmacopeia.

Table 2. Composition of various HCE tablet formulations

Formulation	HCEP	Avicel pH101®	Emcompress®	Purified Talcum	Magnesium Stearate	Ac-Di-Sol®	Explotab®	Aerosil 200®
	Composition (%)							
1	80	16	1.6	2	0.4	-	-	-
2	80	16	-	2	0.4	1.6	-	-
3	80	16	-	2	0.4	-	1.6	-
4	80	12	-	4	0.4	-	1.6	2
5	80	16	-	2	0.4	-	-	1.6
6	80	13.6	-	2	0.4	1.6	-	2.4
7	80	16	-	2	0.4	-	1.6	-
8	80	12	-	4	0.4	-	1.6	2
9	80	12	-	4	0.4	-	1.6	2

Note: SMCC90: HC extract ratio were 3:1 for formulation 1-4, 2:1 for formulation 5-8 and 4:1 for formulation 9.

Quality controls of HCEP, bulk powder and HCE tablets

Quality control of HCEP

The moisture content (%LOD) and flowability of HCEP were determined according to methods described in USP25/NF18.

Quality control of bulk powder

The moisture content, bulk density, tapped density, compressibility ratio and flowability of HC bulk powder were determined.

Quality control of HCE tablets

HCE tablets were subjected to determination of weight variation, hardness, friability and disintegration time according to USP25/NF18. Profile and stability of active compounds in HCE tablet extract were evaluated by chromatographic techniques, using rutin and quercetin as markers.

Stability tests of HCE tablets

HCE tablets were stored at RT and 45˚C for 3 months. At the end of each month, tablets stored at 45˚C were sampled and the weight variation, hardness, friability, and disintegration time were determined. Tablets stored at RT were analyzed at the end of the 3rd month. Chemical stability was also assessed by thin-layer chromatographic (TLC) analysis.

Statistical analysis

The data are presented as mean±S.D. while Pearson correlation coefficient, means, standard deviations (S.D.) and statistical differences were evaluated through two-way analysis of variance (ANOVA). The SPSS software package (Version 11.0, Chicago, IL) was used for the analysis with p value <0.05 as statistical significance.

RESULTS AND DISCUSSION

Preparation of HCE

HCE was prepared from aerial parts of HC plants, which were reported to contain high levels of flavonoid-glycosides (Eui et al., 1996; Bansiddhi et al., 2003). HCE appeared as dark-green, highly viscous liquid with unique odor. The yield was 5.85% based on dried HCP.

Calculation of HCE weight in tablets

One 350-mg capsule of GPO NaturePlex® composed 65.3% of five herbal extracts: *Borassus flabellifer* Linn., *Houttuynia cordata* Thunb., Randia *siamensis* Craib., *Combretum quadrangulare* Kurz. and *Mimusops elengi* Linn. HC extract accounted for 7.69% of total extract. Since the recommended dose was 2 capsules per day (Sriwanthana et al., 2007), the amount of HC extract per day was 35.16 mg. A no.0 capsule, which holds an average of 278.46 mg HC powder (data not shown), contains an equivalence of 16.38 mg HCE based on a 5.85% yield.

Development of HCE tablets

Preparation of HCEP

Despite high ratio of extract-to-adsorbent, HCEP obtained from formulations 1 and 2 exhibited poor appearance and flow property. At lower ratio in formulations 3-5, wetness was observed and production of granules was difficult. Corn starch is known to be a primary excipient for oral solid dosage form and a common absorbent in pharmaceutical products (Rowe et al., 2003), with adsorption ability resulting from the interaction between free hydroxyl groups (OH) in glucose unit and water molecules via hydrogen bond (Beery and Ladisck, 2001). However, this interaction occurred only on the surface (van den Berg et al., 1975; Beery and Ladisck, 2001) and thus, a high amount of corn starch was required to obtain HCEP with proper characteristics. In contrast, formulations 6 and 7 which utilized SMCC90 as adsorbent showed better results. This is in agreement with a report by Rowe et al., (2003) which suggested the use of SMCC90 as filler for both capsule and tablet forms to improve the compressibility in wet-granulation and direct compression. SMCC90 was obtained from silicification of 2% colloidal silicon dioxide (CSD) and 98% microcrystalline cellulose (MCC). Although its polymorphism, porosity and particle size were not different from those of MCC (Tobyn et al., 1998; Luukkonen et al., 1999), the surface area of SMCC90 was five times higher than that of MCC. SMCC90 was a more effective adsorbent than corn starch because CSD on SMCC90 possessed high affinity sorption sites

(Kachrimanis et al., 2000). The surface area of CSD in SMCC90 was at 50-380 m2/g (BET method) while that of corn starch was 0.41-0.43 m2/g. In addition, corn starch was insoluble in both cold water and cold 95% ethanol while SMCC90 was soluble in water, organic solvent and acid (Rowe et al., 2003). As a result, less amount of SMCC90 was required to obtain similar HCEP compared to the use of corn starch. This allowed the formulation of smaller size tablet with the same or higher amount of HCE. Formulation 6 was the least ratio of HCE on adsorbent to completely adsorb and showed a good appearance as powder (Table 3), although the flowability remained poor and required further improvement in the formulation process.

Table 3. Appearances of adsorbed HCE formulations (HCEP)

Formulation	Appearance of HCEP
1	powder, poor flowability, light green
2	powder, very poor flowability, green
3	dried granules, soft, very poor flowability, dark green
4	dried granules, soft, very poor flowability, dark green
5	dried granules, hard, passable flowability, dark green
6	powder, poor flowability, dark green
7	powder, poor flowability, green

Based on the appearance of HCEP, formulations 4, 6 and 7 were selected for further study (Figure 2). Each formulation was tabulated via hydraulic press with 1- and 2-ton forces. Tablets of formulation 4 appeared too soft as the hardness was immeasurable while tablets of formulation 6 and 7 achieved acceptable hardness. The results also suggested that SMCC90 helped increase the tablet hardness (Table 4).

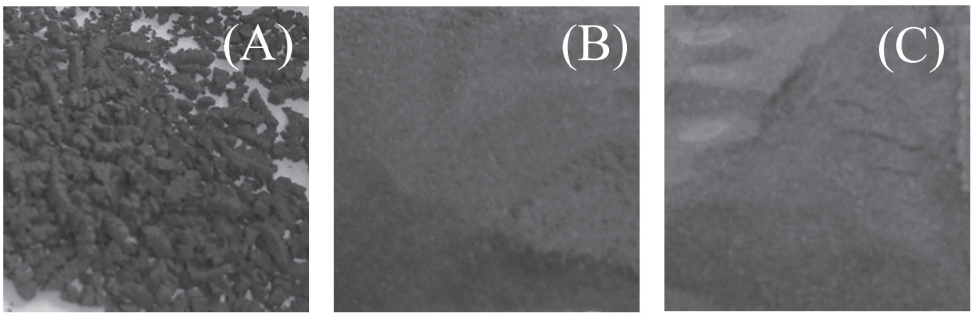

Figure 2. HCEP formulation 4 (A), 6 (B) and 7 (C)

Table 4. Hardness of HCEP tablets without addition of other excipients (mean±S.D.)

Formulation	Compression Force (Ton)	Hardness (N)
4	1	NA
	2	NA
6	1	32.80±03.11
	2	30.10±00.00
7	1	53.95±08.84
	2	48.60±10.64

NA – not applicable, due to tablet softness

Formulation of HCE tablets

Due to poor flowability and compaction properties of HCEP, addition of pharmaceutical excipients was required to enhance powder properties suitable for direct compression. These added excipients were chemically inert, causing neither interaction with nor decomposition to the active ingredients in the extract (Jivraj et al., 2000). In the formulation, microcrystalline cellulose (Avicel PH101®) was used as binder/disintegrant. A study by Palma et al., (2002) on a formulation of tablet from plant extract showed that Avicel PH101® facilitated the disintegration of tablets. Dibasic calcium phosphate (Emcompress®), with a good flowability and compact property was utilized as glidant (Rowe et al., 2003). Magnesium stearate served as lubricant and antiadherent (Eilalifa et al., 2009). Sodium carboxymethyl starch (Explotab®) or crosslinked sodium carboxymethylcellulose (Ac-Di-Sol®) was employed as superdisintegrant. Purified talcum possessed lubricating and antiadherent properties. Colloidal silicon dioxide (Aerosil 200®) was used as glidant and antiadherent to improve flowability and content uniformity of pre-compressed powder (Gierer, 2002; Rowe et al., 2003; Teng et al., 2009). A decrease of Avicel PH101® and increases of purified talcum and addition of Aerosil 200® in formulation 4, resulted in tablets with higher hardness and longer disintegration time (>15 min) than other formulations. Tablets of formulations 8 and 9 appeared to have acceptable hardness, disintegration time (<15 min) and friability (<1%) (USP25/NF18). The properties of formulated tablets are compiled in Table 5.

Table 5. Hardness, disintegration time and friability percentage of HCE tablets

Formulation	Hardness (N)	Disintegration time (min)	% Friability
1	47.28±5.39	2.55	ND
2	31.72±2.56	0.35	ND
3	54.37±2.75	1.52	ND
4	97.06±8.53	>15	ND
5	21.61±2.62	1.02	ND
6	23.76±3.36	0.45	0.06
7	14.44±1.71	0.18	0.22
8	22.15±1.70	6.32	0.08
9	57.98±7.60	2.18	-0.04

ND – not determined

Quality controls of HCEP, bulk powder and HCE tablets

Quality controls of HCEP and bulk powder

The moisture content of bulk powder was 37.6% lower that of HCEP (Table 6). High moisture content of herbal tablets was reported to associate with the growth of microorganisms and possibility of degradation of active compounds (Sitthichai, 2004). Lower moisture content also contributed to the improvement of the flow property as evidenced by a significant decrease in the angle of repose. The compressibility ratio of bulk powder was within a range (5-12%) that suggested excellent flowability. The properties of this bulk powder appeared to be suitable for direct compression (Jivraj et al., 2000).

Table 6. Quality controls of HCEP and bulk powder

Test	HCEP	Bulk powder
LOD (%)	5.29	3.30
Bulk density	-	0.398
Tapped density	-	0.431
Compressibility ratio (%)	-	7.609
Repose angle (˚)	46.20±4.80	28.10±2.60

Quality controls of HCE tablets

Weight variation of HCE tablets was within the range (USP25/NF18), thus ensured the consistency of the amount of active compounds of HCE tablets. The hardness of tablets was invariable. The friability and disintegration time were less than 1% and 15 min, respectively (Table 7), both were also within acceptable range (USP25/NF18). These parameters are important in commercialized process as they directly influenced the quality and shelf-life of the products (Sitthichai, 2004).

Table 7. Quality controls of HCE tablets

Weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (N)	Friability (%)	Disintegration time (min)
250.26±0.73	8.51±0.01	3.40±0.01	41.50±3.20	0.04	1.23

Data are expressed as mean±S.D.

Stability tests of HCE tablets

Stability test of HCEP and bulk powder

Under both 45˚C and RT storage conditions, storage time affected the moisture content of HCEP and bulk powder. The longer the storage time, the lower the moisture content (Table 8). Compared to the value on 0 month (Table 6), % LOD of HCEP kept for 3 months at 45˚C and RT were decreased 58.6 and 59.7%, respectively. The trend also applied to the bulk powders, in which the decreases were 33.6 and 37.6% for the 3-month storage at 45˚C and RT, respectively. The appearances of the HCEP and bulk powder remained unchanged. In the 1st month period, the rate of moisture evaporation was the highest especially at 45˚C. This was because HCEP and bulk powder were exposed to a relatively high temperature, thus a rapid transfer of moisture within the system occurred to balance the temperature. As the temperature of the samples were in equilibrium with the storage system, the rate of moisture evaporation decreased (2nd and 3rd month) (Sirithunyalug et al., 2008).

Table 8. Moisture content (%LOD) of HCEP and bulk powder

Conditions		HCEP	Bulk powder
45˚C	1 Mo	2.71	2.64
	2 Mo	2.43	2.50
	3 Mo	2.19	2.19
RT	3 Mo	2.13	2.06

Stability of HCE tablets

Quality controls of HCE tablets after stability test are presented in Table 9. Compared to the data of 0-month tablets (Table 7), the weights of tablets were not significantly different as the storage time was extended. Storage conditions showed no effect on the weight and friability of tablets. In contrast, the hardness of tablets stored at 45˚C was affected by the storage time. The hardness of tablets was significantly decreased after one month of storage and continued to slowly but significantly decrease as the storage time was extended. This was in concurrent with a slight decrease in disintegration time of tablets after 2 months which suggested a possibility of tablets taking up moisture, resulting in a more water-penetrable structure and a more rapid disintegration rate. A significant increase in disintegration time of tablets stored at RT for 3 months was also a result of an increase in the hardness of tablets.

Table 9. Quality controls of HCE tablets after stability test

Conditions		Weight (mg)	Dimension (mm)	Thickness (mm)	Hardness (N)	Friability (%)	Disintegration time (min)
	1 Mo	246.96±1.17	8.50±0.00	3.43±0.02	37.50±2.10	0.01	1.20
45˚C	2 Mo	246.13±1.48	8.52±0.01	3.43±0.01	36.50±1.00	-0.01	1.25
	3 Mo	245.76±1.10	8.51±0.01	3.43±0.02	34.70±1.00	-0.20	1.02
RT	3 Mo	246.84±1.22	8.49±0.02	3.37±0.01	44.90±4.20	-0.07	2.18*

Data are expressed as mean±S.D., (*p<0.05)

Stability of chemical components in HCE tablets was tested by TLC analysis using rutin and quercetin as standard markers. Tablet extracts showed TLC profiles that were practically identical to that of the crude extract, at both RT and 45˚C during the 3-month storage, suggesting that no degradation or decomposition of the extract components occurred (Figure 3). This is in part due to the elimination of solvent from the extract to prevent chemical reaction and the minimization of moisture content in the adsorption step which prevented the growth of microorganisms that could lead to fermentation and chemical decomposition (Sitthichai, 2004). The results also verified the compatibility between the chemical components in the extract and the excipients used in the formulation of tablets.

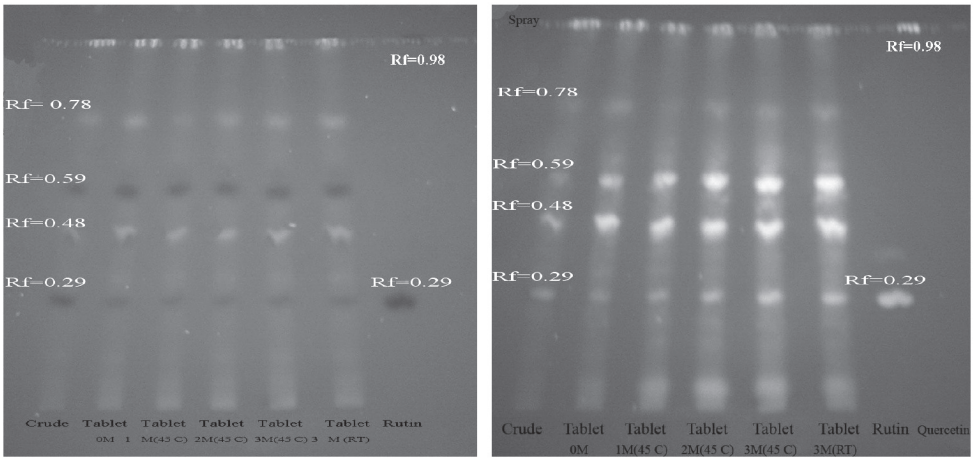

Figure 3. TLC chromatograms of HCE tablet extracts, compared with crude extract and standards. Chromatograms are visualized under UV-254 nm (A) and UV-365 nm (B). Lane 1: crude HCE, Lane 2: HCE tablet extract 0th Mo at 45˚C, Lane 3: HCE tablet extract 1st Mo at 45˚C, Lane 4: HCE tablet extract 2nd Mo at 45˚C, Lane 5: HCE tablet extract 3rd Mo at 45˚C, Lane 6: HCE tablet extract 3rd Mo at RT, Lane 7: rutin standard, Lane 8: quercetin standard.

CONCLUSIONS

Formulation of physically- and chemically-stable *H. cordata* extract (HCE) tablets was accomplished. Preparation of the plant extract eliminated microbial contamination from the raw materials and the active components can be concentrated to as high as 4 folds compared to that of a HCP capsule. Standardization of the extract with chromatographic methods using flavonoid standards as markers allowed the preparation of uniformed, consistent and reproducible HCE tablets. Selection of an appropriate adsorbent, in this case SMCC90, aided the conversion of viscous, sticky plant extract into low moisture, compressible powder. With the addition of other suitable pharmaceutical excipients, powder with good flowability and compressibility was obtained for manufacturing of HCE tablets with good appearances and disintegration. The prepared tablets showed good stability at both RT and at 45˚C conditions over the period of 3 months. HCE tablets can be used as a food supplement to replace the traditional powder capsules. The process and techniques from this study can also be employed in the development of other medicinal plant extract tablets.

ACKNOWLEDGEMENTS

This research is supported by a TRF-Master research grant from the Thailand Research Fund (WI515S149) in collaboration with the Defence Pharmaceutical Factory (DPF), Defence Industry and Energy Center, Office of Permanent Secretary of Defence.

REFERENCES

Bansiddhi, J., Y. Techadumrongsin, K. Anulukkhanapakorn, B. Sriwanthana, T. Boonrod, S. Chairach, P. Wongsinkongmun, D. Pattamadilok, and J. Mingmeung. 2003. *Houttuynia cordata* Thunb. Research Institute, Department of Medical Science, Nontaburi.

Beery, K.E., and M.R. Ladisch. 2001. Chemistry and properties of starch based desiccants. Enzyme and Microbial Technology 28: 573–581.

Díaz, L., C. Souto, A. Concheiro, L.M. Gomez-Amoza, and R. Martinez-Pacheco. 1996.

Evaluation of Eudragit E as excipient in tablets of dry plant extracts. S.T.P. Pharma 6 (2); 105–109. Eilalifa, A. E. O.; D.M.R. Georget, S.A. Barker and P.S. Belton. 2009. Study of the physical properties of kafirin during the fabrication of tablets for pharmaceutical applications. Journal Cereal Science 50: 159–165.

Eui, S., S. Toshiro, K. Tomoko, H. Youich, N. Yukio, Y. Masashi, and T. Toshihiro. 1996. Pharmacognostical studies of houttuyniae herba (2) Growth and flavonoid glycoside contents of *Houttuynia cordata* Thunb. cultivated under shade condition. Natural Medicines 50(1): 45–48.

Formica, J. V., and W. Regelson. 1995. Review section: Review of the biology of quercetin and related bioflavonoids. Fd Chem. Toxic. 33(12):1061–1080.

Gierer, D.S. 2002. Method for manufacturing a low dose pharmaceutical composition having uniform drug distribution and potency using silicon dioxide, WO Patent 2002087546.

Havsteen, B. H. 2002. The biochemistry and medical significance of the flavonoids. Pharmacology and Therapeutics 96: 67-202.

Jivraj, M., L. G. Martini, and C. M. Thomson, 2000. An overview of the different excipients useful for the direct compression of tablets. PSTT 3(2): 58–63.

Kachrimanis, K., M.F. Noisternig, U.J. Griesser, and S. Malamataris. 2000. Dynamic moisture sorption and desorption of standard and silicified microcrystalline cellulose. European Journal of Pharmaceutics and Biopharmaceutics 64: 307–315.

Kim, I.S., J. Kim, J. S. Kim, C. Yun, D. Kim, and J. Lee. 2007. The inhibitory of Houttuynia cordata extract on stem cell factor-induced HMC-l cell migration. Journal of Ethnopharmacology 112: 90–95

Lau, K.,K. Lee, C. Koon, C.S. Cheung, C. Lau, H. Ho, M.Y. Lee, S.W. Au, C.H. Cheng, C.B. Lau, S.K. Tsui, D.C. Wan, M.M. Waye, K. Wong, C. Wong, C.W. Lam, P. Leung, and K. Fung. 2008. Immunomodulatory and anti-SARS activities of *Houttuynia cordata*. Journal of Ethnopharmacology 18(1): 79–85.

Li, X. 2003. A preparation containing the total flavonoids and polysaccharides from *Houttuynia cordata* thumb. for improving gastrointestinal function and resisting mutation, and its preparation method, CN patent 1457810.

Lu, H.M., Y.Z. Liang, L.Z. Yi, and X.J. Wu. 2006. Anti-inflammatory effect of *Houttuynia cordata* injection. Journal of Ethnopharmacology 104: 245–249.

Luukkonen, P., T. Schæfer, L. Helle′n, A.M. Juppo, and J. Yliruusi. 1999. Rheological characterization of microcrystalline cellulose and silicified microcrystalline cellulose wet masses using a mixer torque rheometer. International Journal of Pharmaceutics 188: 181–192.

Matsui, J., N. Kiyokawa, H. Takenouchi, T. Taguchi, K. Suzuki, Y. Shiozawa, M. Saito, W. Tang, Y.U. Katagiri, H. Okita, and J. Fujimoto. 2005. Dietary bioflavonoids induce apoptosis in human leukemia cells. Leukemia Research 29: 573–581.

Palma, S., C. Luján, J.M. Llabot, G. Barboza, R.H. Manzo, and D.A. Allemandi. 2002. Design of *Peumus boldus* tablets by direct compression using a novel dry plant extract. International Journal of Pharmaceutics 233: 191–198.

Plazier-Vercamen, J.A., and C. Bruwier. 1986. Evaluation of excipients for direct compression of the spray-dried extract of *Harpagophytum procumbens*. S.T.P. Pharma 2 (17): 525–530.

Renoux, R., J.A. Demazieres, J.M. Cardot, and J.M. Aiache. 1996. Experimentally designed optimisation of direct compression tablets. Drug Dev. Ind. Pharm. 22 (2): 103–105.

Rowe, R. C., P.J. Sheskey, and S.C. Owen. 2003. *Handbook of Pharmaceutical Excipients*. Pharmaceutical Press and American Pharmaceutical Association, London.

Sandhu, K.S., and N. Singh. 2007. Some properties of corn starches II: Physicochemical, gelatinization, retrogradation, pasting and gel textural properties. Food Chemistry 101: 1499–1507.

Sirithunyalug, J., S. Yotsawimonwat, S. Okonoki, P. Leesawat, N. Kittipongpatana, and O. S. Kittipongpatana. 2008. Pharmaceutical Technology I. Chiang Mai: Faculty of Pharmacy, Chiang Mai University.

Sitthichai, N. 2004. Original article; Herbal standard in Thai herbal pharmacopoeia. Thai Journal of Phytopharmacy 11(1): 21–32.

Sriwanthana, B., W. Treesangsri, B. Boriboontrakul, and P. Chavatitumrong. 2007. In vitro effect of Thai medicinal plants on human lymphocyte activity. Songklanakarin Journal of Science and Technology 29 (1): 17–28.

Teng, Y., Z. Qui, and H. Wen. 2009. Systematical approach of formulation and process development using roller compaction. European Journal of Pharmaceutics and Biopharmaceutics 73: 219–229.

Tobyn M. J., G.P. McCarthy, J.N. Staniforth, and S. Edge. 1998. Physicochemical comparison between microcrystalline cellulose and silicified microcrystalline cellulose. International Journal of Pharmaceutics 169: 183–194.

USP 25/NF 18. The United States Pharmacopeial Convention, MD, USA.

Van den Berg, C., F.S. Kaper, J.A.G. Weldring, and I. Wolters. 1975. Water binding by potato starch. Journal of Food Technology 10:589–602.

Wagner, H., S. Bladt, and E.M. Zgainski. 1990. Plant drug analysis. Berlin: Springer-Verlag, pp. 19–23, 163–173, 303–304.

Xuan, Z., and J.A. Lui. 2004. Traditional Chinese medicinal buccal tablet for treating acute and chronic pharyngitis and stomatitis and its preparation method, CN patent 1485081.

Yu, W. 2007. Manufacture of traditional Chinese medicinal composition for treating asthma, CN patent 1954854

Zhang, T., and D. Chen. 2008. Anticomplementary principles of a Chinese multiherb remedy for the treatment and prevention of SARS. Journal of Ethnopharmacology 117: 351–361.