CHAPTER 2

Literature review

2.1 Alternative medicines

The word “alternative”, when functioning as an adjective, means “different from usual or conventional” [8]. Thus, the meaning of alternative medicines can be “the medicines that are not usual for the majority of people in certain area” [9]. In term of the meaning, it is possible that the definition of alternative medicine can be changed by the trend, place and time. For example, in Thailand during the time of the reign of King Rama 4th, western medicine was brought into Thailand and considered “alternative medicine” for that time [9]. In 2001, World Health Organization (WHO) defined the definition of alternative medicine as “Complementary and Alternative Medicine (CAM)”, which is that “The term CAM often refers to a broad set of health-care practices that are not part of a country’s own tradition and are not integrated into the dominant health-care system. Other terms are sometimes used to describe these health-care practices including ‘natural medicine’, ‘non-conventional medicine’ and ‘holistic medicine’” [9].

In Thailand, the definition of alternative medicines often refers to “the medicines that are not modern medicine, Thai traditional medicine and Thai indigenous medicine. Other medicines are considered alternative medicines in Thailand.” [9]

Alternative medicines can be categorized by many methods. According to the separation by National Center of Complementary and Alternative Medicine (NCCAM), there are 5 categories of alternative medicine [9] as follows;

- **Alternative Medical Systems**: Alternative medicines that use many methods to diagnose and treat the illness, such as Traditional Chinese Medicine.
- **Mind-Body Interventions**: Alternative medicines that treat a patient with physical and metal activities, such as yoga.
- **Biologically Based Therapies**: Alternative medicines that treat a patient by using biological or chemical substances, such as vitamins and herbs.
- **Manipulative and Body Based Methods**: Alternative medicines whose treatment is done by manipulative skills, such as massage.
- **Energy Therapies**: Alternative medicines that treat a patient by using measurable or immeasurable energy, such as Reiki.

2.2 Traditional Chinese Medicine

It can be said that Traditional Chinese Medicine (TCM) "is one of the oldest healing systems in the planet." [10] According to the holistic concept, TCM has 4 main principles [10];

- **The body is an integrated whole.** : Physique, mind and spirit in one body cannot be separated as they have effects on one another.
- **Humans are completely connected to the nature.** : Changes in the nature such as season or geographical location have effects on human body.
- **Humans were born with a natural self-healing ability.** : As the nature has regenerative capacity, humans do too.
- **Prevention is the best cure.** : Human body is continually showing signs of the state of health. Humans can prevent illness by understanding these signs.

According to TCM, every illness is caused by the loss of the balance between Yin-Yang (阴−阳). The Yin-Yang theory explains that everything in the universe consists of hot energy (Yang/阳) and cold energy (Yin/阴) in the balanced condition. If the balance is interfered, the changing of nature will occur. For humans, this changing

means illness [11-14]. According to the Yin-Yang theory, TCM categorizes elements of body organs into 5 elements, which are water, wood, fire, earth and metal [11-13, 15].

There are 4 main diagnosis methods in TCM [16];

- **Observation**: Observing patient's physical expression, color of the skin, appearance of the body and tongue coating
- **Listening and smelling**: Listening to the patient's voice and smelling the body odor.
- **Inquiring**: Inquiring the disease condition, duration, etc
- **Palpation**: Feeling the pulse to determine its quality, power, rate, rhythm and also palpating the body for any suspicion.

There are 5 main methods for treatment in TCM [10, 17] as follows;

- **Acupuncture**: The use of needles to stimulate Qi energy to activate the self-healing system of the body.
- **Acupressure**: The same concept as acupuncture but done by physical pressure instead of needles.
- **Classical herb therapy**: The use of herbs to balance Yin-Yang or Five elements when getting sick.
- **Eating for healing**: The concept of preventing illness by using food as medicine to balance Yin-Yang or Five elements before getting sick.
- **Qigong**: The physical and mental activities to stimulate Qi energy by breathing and physical movements.

2.3 Menopause disorder: symptoms, conventional treatment and adverse effects

When women reach the period when their reproductive ability is over, the menstrual cycle stops. This condition is referred to as menopause. Menopause disorder

(also called “menopausal syndrome”) is a group of symptoms (Table 2.1) found in some women those are in the perimenopause period (immediately the first year before and right after the menopause) because of changing of women’s sexual hormone level [7, 18-19]. The symptoms do not appear throughout of life and do not cause mortality but they affect patients’ quality of life [7, 18-19]. There are two conventional treatments of these symptoms, Hormone Replacement Therapy (HRT) and taking the Selective Estrogen Receptor Modulators (SERMs), both of which can cause long term adverse effects (Table 2.2) [7].

Table 2.1: Clinical presentation of menopause disorder [7]

Signs		Symptoms
Perimenopause	Menopause	
Dysfunctional uterine bleeding as a result of anovulatory cycles	Signs of urogenital atrophy	Vasomotor symptom (hot flush, night sweat)
		Sleep disturbances
		Mood changes
		Sexual dysfunction
		Problem with concentration and memory
		Vaginal dryness and dyspareunia

Table 2.2: Long term adverse effects in menopause disorder conventional treatments

	Cardiovascular disease	Breast cancer	Ovarian cancer	Endome-trial cancer	Venous thrombo-embolism	Gallbladder disease
HRT	✓	✓	✓	✓	✓*	✓**
SERMs	✓***	✗	n/a	n/a****	n/a	✗

✓ = the treatment will cause the adverse effect
✗ = the treatment will not cause the adverse effect
n/a = data about the risks are not available
*High dose can increase the risk but low dose can decrease.
**Only oral route can increase the risk.
***Raloxifene does not significantly affect the risk.
****Tamoxifen may increase the risk. [20]

The vasomotor symptom is the most commonly symptom found in more than 25% of women who reach to the perimenopause. Estrogens decrease hot flushes in most women, and all types and routes of administration of estrogen are equally effective [7].

There are also non-hormonal therapies such as use of Fluoxetine and Venlafaxine for treatment of the symptom but there are also side effects such as insomnia, Gastrointestinal (GI) disturbance [7].

At the present, patients and health-care staff can easily access the information about menopause's adverse effects so there have been considerations about the risks and benefits of conventional treatment [7, 21]. As a result, many alternative treatments of the symptoms, such as TCM, have been considered [22].

2.4 TCM and Menopause disorder

In TCM, there are two kidneys those are kidney Yin (Shen Yin/肾阴) and kidney Yang (肾阳) (Figure 2.1) [12-13, 21]. Kidney Yang is imagined as the driving forces of all metabolic process [21]. In this process endpoint is the production of kidney Yin that is constitutes the "structive potential" for the production of kidney Yang.

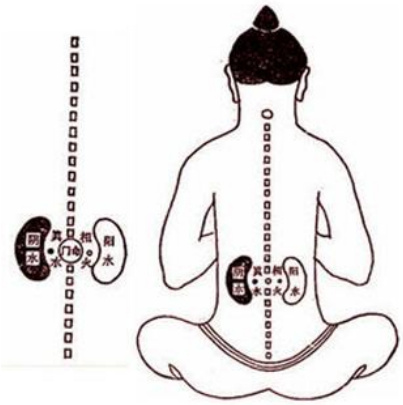

Figure 2.1: Kidney Yin (Black) and kidney Yang (White) in human body according to TCM theory (picture from http://www.sldint.com/a/herbal_healthcare/methodical-idea-of-kidney-function.html; accessed 31 January 2014)

There are three theoretical cornerstones in TCM, Jing (精), Qi (氣), and Shen (神), those are called "Three treasures (三寶/Sanbao)" [23-24]. The "structive

potential" (Jing) is said to be the material basis for the physical body and is Yin in nature that means it nourishes, fuels and cools the body. There are two kinds of Jing those are Jing that is inherited from parents in fix amount (prenatal Jing) and Jing that is acquired from food and various forms of stimulation such as exercise, study, meditation, etc (postnatal Jing) [25-27]. Jing is stored in kidney and used to produce the energy (Qi) by kidney Yang [21, 27]. Qi will provide energy to the mind, resulting in the consciousness of the spirit (Shen/神) (Figure 2.2) [24, 26-28] to allows human body to grow up [21]. As above, it can be said that Jing is Yin, Qi is Yang and Shen is life [23-24, 27].

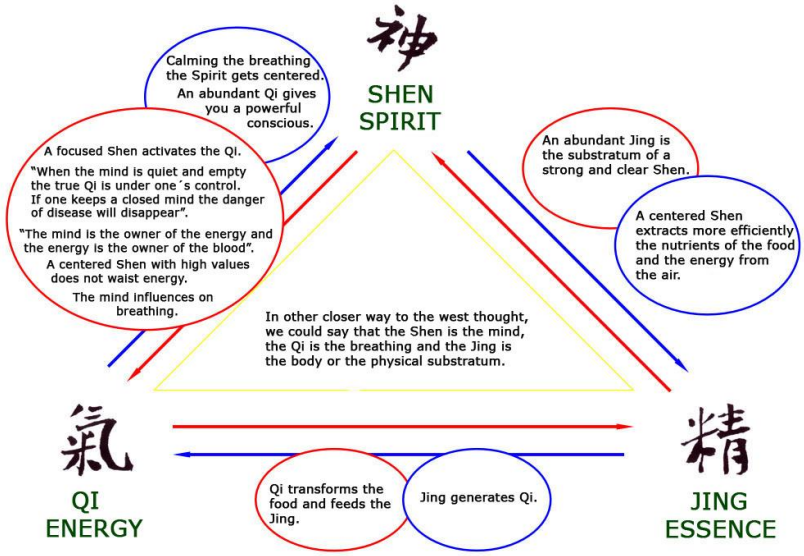

Figure 2.2: The connection of Jing, Qi and Shen (picture from http://test.luohan.com/medical-luohan/jing_qi_shen_english-3/; accessed 31 Jan 2014)

TCM explains that the aging of human body is caused by the decrease of Jing. This affects the function of both kidney Yin and kidney Yang and causes the decrease of Yin and Yang of whole body [21].If Yin declines faster than Yang, the symptoms of Yang excess (hot flushes, palpitations, insomnia, forgetfulness, dryness) will show. In contrast, Yin excess' symptoms such as fatigue, depression, chilliness, edema can be detected when Yang decreases more rapidly [13, 21].

In terms of symptoms, the clinical presentation of menopause disorder is similar to that of the aging concept of TCM. Thus, it is possible to conclude that menopause disorder is caused by the deficiency of kidney. Therefore, the main treatment in TCM in menopause is to tonify the kidney and Jing [12, 21, 29]. In west, because of hot flush is the mostly symptom found in patients with menopause disorder, therefore Yin deficiency has come to be seen as definition of menopause disorder by western TCM practitioners [21, 30].

2.5 Liu Wei Di Huang

Of all the top 10 mostly used Chinese herbal formulas to treat menopausal syndrome in Taiwan (2002) [31] and Chinese herbal formulas mostly used in Thailand [32], Liu Wei Di Huang (Six ingredients with rehmaniae/六味地黄/LWDH) is one of TCM herbal formulas used to treat menopause disorder related to kidney Yin deficiency with the mechanism of nourishing yin and invigorating the kidney. This formula also has indication for treatment of waist and knee weakness, vertigo, tinnitus, deafness and diabetes [21, 31-33]. The ingredients of the formula are six crude drugs, which are Shudihuang, Shanzhuyu, Shanyoa, Zexia, Fuling and Danpi [2, 21, 31-34] (Figure 2.3). The crude drugs' proportion, roles and activities in this formula are listed below [32-33] (Table 2.3).

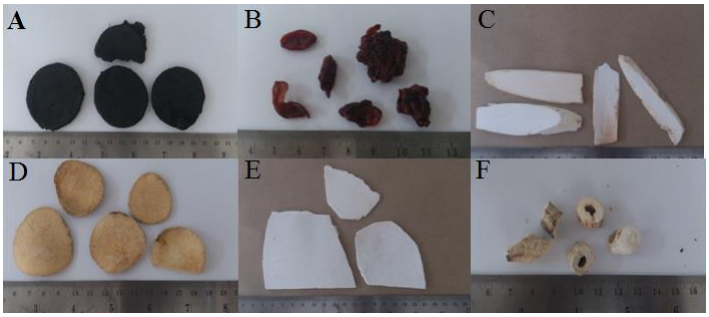

Figure 2.3: Six crude drugs of LWDH formula; Shudihuang/熟地黄 (Radix rehmanniae praeparata) (A), Shanzhuyu/山茱萸 (Fructus corni) (B), Shanyao/山药 (Rhizoma dioscoreae) (C), Zexia/泽泻 (Rhizoma alismatis) (D), Fuling/茯苓 (Poria) (E) and Danpi/丹皮 (Cortex moutan radicis) (F)

Tables 2.3: Details of crude drugs of LWDH formula [32, 34]

Crude drug	Proportion by weight	Activities
Shudihuang	24	Enrich the blood, nourish Yin, supplement Jing
Shanzhuyu	12	Invigorate the liver and kidney, astringe and preserve Jing
Shanyao	12	Invigorate the spleen and stomach; promote production of body fluid and benefit the lung, invigorate the kidney, preserve Jing
Zexia	9	Promote dieresis to resolve dumpness from the lower energizer and expel the heat
Fuling	9	Promote dieresis to resolve dumpness from the lower energizer, invigorate the spleen, tranquilize the mind
Danpi	9	Clearly away heat, cool and circulate the blood to remove blood stasis

According to Pharmacopoeia of the People's Republic of China (2005)[2], there are 2 official preparations of LWDH, Liu Wei Di Huang Wan (六味地黄丸 /LWDHW) and Liu Wei Di Huang Keli (六味地黄顆粒/LWDHK). The formula can be prepared in the forms of pills (Wan/丸 = Pill) and granules (Keli/顆粒 = Granule), with dose of 6 – 9 grams and 3 – 5 grams for 2 – 3 times a day, respectively. The data about the extraction study of this formula are very limited. Only the decoction of the formula has been recorded in TCM textbooks [32-33].

In general, there have been some problems concerning the quality of Chinese products. TCM has been under control, banned or warned in many countries [3-6] with the reason of quality, such as the increase of regulation for importing Chinese herbs in Taiwan [6] and the recall of twelve dietary supplements of TCM in USA [3]. In Denmark, LWDH formula is warned by Danish Food Administration (DFA) due to the contamination of dangerous ingredients [5]. As a result, these incidents have sabotaged the reliability and creditability of the formula among the health staff and the patients.

2.6 Evaluation of quality of herbal materials

In term of the quality of herbs, there are some parameters for evaluation, which can be based on 2 topics [2, 35-36];

2.6.1 To identify the herbal materials

The purpose of this topic is to ensure that the acquired herbal materials meet the requirement. The identification can be carried out by physical and chemical methods.

1) Physical identification: Physical identification is the first step towards establishing the identity and degree of purity of such material. This should be carried out before any further tests are undertaken. The physical identification is the method for identify the characteristic of herbal materials by examination of macroscopic and microscopic of the material.

2) Chemical identification: Chemical identification is methods those were designed to determine the phytochemical identity of herbal materials. The determination can be carried out by any phytochemical reactions (e.g. detection of alkaloid by using Dragendoff reagent) or any chromatographic techniques (e.g. thin layer chromatography (TLC)).

2.6.2 To evaluate the quality of herb materials [36]

The purpose of this topic is to evaluate the herbs in any parameters to justify their quality. The followings are some parameters those most be found in monographs of herbal pharmacopoeia;

1) Water content: An excess of water in herbal materials will encourage microorganism growth and deterioration following hydrolysis. Therefore, limit of water content is normally found in monographs. The water determination methods those most be found in monographs are azeotropic method (e.g. toluene distillation) and loss on drying method.

2) Ash content: Ash content is residue of herbal material after ignition. Ash content determination methods those most be found in monographs are;

- Total ash: The method that is designed for measurement of total amount of material remaining after ignition. It includes both "physiological ash" (Ash which is derived from plant tissue itself) and "non-physiological ash" (Ash of the residue of extraneous matter such as sand and soil adhering to the plant surface).
- Acid-insoluble ash: The method that is used after determination of total ash for measurement of the amount of silica present (esp. sand and siliceous earth). Acid-insoluble ash is the residue obtained after boiling total ash with dilute hydrochloric acid and ignition the remaining insoluble matter.

3) Extractive value: Extractive value (also can be called % extractive) is the amount of active constituents those are extracted with solvents from a given amount of herbal material. The most extraction methods those can be found in monographs are cold maceration and hot extraction.

4) Chemical assay: Chemical assay is the analysis of chemical markers those were found in herbal materials. Analytical methods can be carried by any methods according to the monographs such as colorimetry, Ultraviolet spectrometry, etc.

2.7 Quality parameters of LWDH crude drugs

For the crude drugs of LWDH, there are monographs showing the quality in Pharmacopoeia of the People's Republic of China (2005) [2] (Table 2.4) but some parameters of some crude drugs are still not available.

Table 2.4: Quality parameter monographs of LWDH Crude drugs

Plant name	Topic							Page
	PD	CI*	WC	TA	AA	EV	CA **	
Shudihuang	✓	✓	×	≤ 6.0%	≤ 2.0%	≥ 60.0%	×	233
Shanzhuyu	✓	✓	≤ 16.0%	≤ 6.0%	≤ 0.5%	≥ 50.0%	≥ 0.6%	91
Shanyao	✓	×	×	×	×	×	×	261-262
Zexie	✓	×	×	≤ 5.0%	≤ 0.5%	×	×	248
Fuling	✓	×	≤ 15.0%	≤ 4.0%	≤ 2.0%	×	×	181-182
Danpi	✓	✓	≤ 13.0%	≤ 5.0%	≤ 1.0%	≥ 15.0%	≥ 1.2%	46-47

Note: PD = Physical description, CI = Chemical identification, WC = Water content, TA = Total ash, AA = Acid-insoluble ash, EV = Extractive value and CA = Chemical assay

✓ = Data Available, × = No Data Available

* Perform by TLC method with standard substances: 5-(hydroxymethyl) furfural for Shudihuang, ursolic acid for Shanzhuyu and paeonol for Danpi

** Perform by HPLC method with standard substances: loganin for Shanzhuyu and paeonol for Danpi

2.8 Pharmaceutical solid dosage form: Powders, Granules and Tablets

2.8.1 Powders and granules

Powders are the most basic dosage form and are the main ingredient used to prepare other dosage forms [37-39]. Definition of powders is “mixtures of very

fine (small particle size), dry, chemical and drugs (Active Pharmaceutical Ingredients/APIs) intended for oral or topical use" [39]. Because of the very fine appearance, powders have some limitations when used to produce other dosage forms (e.g. dusting, cohesivity, electrostatic charge).

Granules are a product derived from powders experiencing the physical aggregating processes (granulation), whose original particles can still be identified for the propose to solve the limitation of powders [37, 40]. Granulation can be achieved with or without using water or other naturally adhesive substances (binder). There are two methods of granulation, dry granulation and wet granulation [37, 40].

1) Dry granulation: Dry granulation involves the process of compacting powder and breaking it. No liquids are required for this process [37, 41]. The process starts by mixing desired powder ingredients. If the binder is required, it is used in a form of a dry powder. Compact the mixture to be a bolus tablets (slugs). Finally, the slugs are force-passed with equipment such as oscillating granulator. Dusting and noise are the major problems of this process.

2) Wet granulation: Wet granulation requires agglomerate powder and the use of water or appropriate solvents and binder [37] to make wet mass before being granulated. The followings are two methods of binder addition.

- A dry binder addition starts from adding and mixing binder as a dry powder to the powder mixture. Then, water or other solvents is added after the mixing to make a wet mass. Then the wet mass is force-passed through an appropriate screen, dried and force-passed the dry granules again to obtain desired size.

- A wet binder addition starts by mixing binder with water or other solvents to produce the solution and add the powder mixture to produce wet mass. The rest of the process is similar to that of the drying binder addition process.

The use of powders and granules as solid dosage form has been replaced largely by the use of tablets and capsules because of their limitations. Nevertheless, they still have advantages and can be used as pharmaceutical dosage forms [37]. Some examples of advantages and limitations of these dosage forms are as follows [37, 39];

Advantages

- For children and patients who have problem swallowing, powders and granules are the best option for solid dosage form.
- In term of surface area, the onset of action in these dosage forms is the fastest and the best of all the solid dosage forms.
- For certain kinds of liquid dosage form that have limitations with their API stability when used with solvent contraction, the preparation of powder or granules as powder/granules for solution/suspension is one of the solutions.
- For the treatment requiring very high/bulky dosage APIs (e.g. laxative), powders and granules are more suitable.

Limitations

- For certain kinds of APIs with taste limitations, it is difficult to find solutions for this problem.
- As the bulky forms, powders and granules are less convenient than tablets or capsules for travelling.
- For some APIs, which have low therapeutic index, powders and granules are the least appropriate choice to develop as finished product.

2.8.2 Tablets

Tablets are the most popular solid dosage form due to many of their prominent points compared with those of the other forms, such as carriage convenience, dosage flexibility (more variety than capsules), ability to hide unpleasant taste and/or odor [37, 40]. In the process of tablets preparation, there are some ingredients called "excipients" those are included in the tablets formulation. General details of pharmaceutical excipients, requirements for tableting, methods of tablets development process are listed below;

1) Pharmaceutical excipients [37]

Excipients are some ingredients, which are required to add to API to improve their ability of dosage form development or to give value added to the finished products. Table 2.5 shows certain types of excipients, examples and functionality required for tablets formulation development.

Table 2.5: Example of excipients in tablets formulation (copied from Mahato RI, Narang AS. *Pharmaceutical Dosage Forms and Drug Delivery* (2009) Page 324)

Functional role	Examples	Functionality
Diluent (Filler)	- Microcrystalline cellulose (MCC/Avicel®) - Lactose monohydrate or anhydrous - Mannitol - Sorbitol	- Add bulk to the dosage form - May contribute to dissolution and disintegration characteristic
Binder	- Polyvinyl pyrrolidone (PVP) - Hydroxypropyl cellulose (HPC) - Starch	- Bind the powder ingredients to form granules for processing
Disintegrant	- Croscarmellose sodium (CCS) - Crospovidone (xPVP) - Sodium starch glycolate (SSG) - Starch	- Disintegrating of the tablet to granules and powders upon coming contract with water

Table 2.5: of excipients in tablets formulation (continued)

Functional role	Examples	Functionality
Glidant	- Colloidal silicon dioxide(Cab-osil®)	- Aid the flow of granules/blend
Lubricant	- Magnesium stearate - Stearic acid - Sodium stearyl fumarate	- Aid the flow of granules/blend and ejection of tablets in tablet press
Coating material	- Hydroxypropyl methyl cellulose (HPMC) - Plasticizer (polyethylene glycol)	- Provide a physical barrier coating on the surface of the compressed core tablets - Hiding the unpleasant taste/odor of the core
Coloring agent	- Iron oxide red and/or yellow - FD&C Blue #6	- Visual appeal of color
Stabilizer	- Antioxidants (e.g. Ascobic acid)	- Stabilization of the API in the dosage form from stress such as oxidation
Sweetener	- Aspartam - Saccharin sodium - Sucralose	- Sweetening to overcome API taste and/or improve palatability for some types of tablets
Flavoring agent	- Proprietary flavors (orange, pine apple, etc)	- Flavoring to overcome API taste and/or improve palatability for some types of tablets

The followings are the explanation of each functional role mentioned in Table 2.5.

1.1) Diluents

Tablet's weight should not be less than 50 mg for patient's handling comfort. For a very low-dose API, diluent (also known as filler) or bulking agent is required to increase overall weight to 50 mg. Commonly used diluents are produced from organic source (e.g. lactose, sucrose, microcrystalline cellulose (MCC/Avicel®), and mannitol) and from inorganic source (e.g. dicalcium phosphate and sodium chloride).

1.2) Adsorbents

For certain APIs that are in fluid form such as oil-soluble API and fluid extracts, solid form transformation is required for tablet formulating. Adsorbents are substances capable of holding fluids resulting in dry state. Examples of the substance are fumed silica, microcrystalline cellulose, kaolin and bentonite.

1.3) Moistening agents

For wet granulation process, liquids are required to produce powder aggregation, such as water, ethanol and isopropanol. All traces of solvent especially alcoholic solvent must be removed during drying.

1.4) Binding agents

Binding agents (also called binder) are substances used to add before tablet compression to promote tablets compressibility and granulation (in case of granulation method). The binder can be added in either dry or liquid form. Most binders are natural polymeric (such as starch paste, gelatin, polyvinyl pyrrolidone (PVP), alginic acid derivatives and cellulose derivatives,). "Type and concentration of binder affect the granule strength, friability and granule growth rate in wet granulation, and ultimately affect the dissolution rate."[37]

1.5) Glidants

Uniformity of flow rate of powders or granules inside the tablets compressor indicates weight uniformity of tablets. Glidants are a group of substances with properties to reduce particular fiction

between powders (or granules) and flow line. Widely used glidants are colloidal silica, starch and talcum.

1.6) Lubricants

Lubricants have many functions in tablet compression. They prevent adherence of powder or granules to the surface of punch face and dies, reduce inter-particle friction and help to smoothly eject tablets from the die cavity. They also enhance the flow property of granules. Commonly used lubricants are magnesium stearate, stearic acid, talcum, PEG and sodium or magnesium lauryl sulfate.

1.7) Disintegrant

Tablets must breakup (disintegrate) when coming in contact with Gastrointestinal (GI) fluid before API dissolves to assure its activities. A group of substances promoting the breakup is called “disintegrants”. Disintegrants are substances with water swelling property (e.g. starch, cellulose derivative, crospovidone and magnesium aluminum silicate), surface tension decreasing property (e.g. sodium lauryl sulfate) or any properties that can cause disintegration (e.g. gas generating property in effervescent system).

1.8) Miscellaneous

Colorants, flavorants, sweeteners and others which increase stability and value added in the finished product.

2) Requirements for tableting

Tableting is the step of compression of powders/granules passing the blending step of API and excipients. The process starts when the blend is fed into the dies by using a hopper. Inside the dies, the blend is pressed into tablets and ejected as finished tablets. (Figure 2.4) [37-39, 42]. To assure high quality tablets, this step requires the following actions;

- Uniformity flow rate of blend when being fed into the die
- Nonsegregation of the blend in the hopper during loading
- Compactibility of the blend in the die during compression
- Nonsticking of the blend to die's wall and surface of punches
- Sufficient cohesion of the blend to form efficient tablets

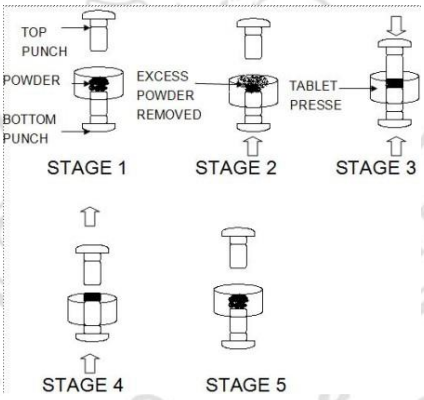

Figure 2.4: Tableting processes (picture from http://www.pharmainfo.net/tablet-ruling-dosage-form-years/operations-involved-tablet-manufacturing; accessed 5 Feb 2014)

3) Methods of tablet development process [37, 42]

For tablet development, tableting steps require good flow ability and compatibility of the blend. Some of APIs have good flow ability and compressibility while some do not. There are 3 general processes in tablets development; direct compression, dry granulation and wet granulation (Table 2.6) [42].

3.1) Direct compression

If powder blend has enough flow ability, compatibility and cohesion with low segregation potential, direct compression is the preferred method. This is the easiest method for tablet development but can be applied only to certain kinds of APIs/excipients.

3.2) Dry granulation

Dry granulation is a preferred method in a situation when compatibility is adequate but powder flow, cohesion and/or segregation potential are inadequate. The method operation is shown in table 2.6.

3.3) Wet granulation

Wet granulation is preferred when compatibility and powder flow, cohesion and/or segregation potential are inadequate (esp. herb extract). The method operation is listed below (Table 2.6).

Table 2.6: Operation involved three methods of tablets development (copied from http://www.pharmainfo.net/tablet-ruling-dosage-form-years/operations-involved-tablet-manufacturing accessed 5 Feb 2014)

Direct compression	Dry granulation	Wet granulation
1. Milling and mixing of APIs and excipients	1. Milling and mixing of APIs and excipients	1. Milling and mixing of APIs and excipients
2. Compression of tablet	2. Compression into slugs or roll compaction	2. Preparation of binder solution
	3. Milling and screening of slugs and compacted powder	3. Wet massing by adding binder solution or granulating solvent
	4. Mixing with lubricant and disintegrant	4. Screening of wet mass
	5. Compression of tablet	5. Drying of the wet granules
		6. Screening of dry granules
		7. Blending with lubricant and glidant
		8. Compression of tablet

2.9 Evaluation of tablets quality for herbal product: Principle of Thai FDA

When herbal materials have been developed into a product, there are some parameters for product safety and efficacy confirmation. For tablets product from herb, there are some quality, efficacy and safety parameters issued by "Thai Food and Drug Administration (Thai FDA)" (Table 2.7) [35, 43].

Table 2.7: Thai FDA principles for herbal tablets

Topics	Parameters	Criteria
Quality and efficacy	Appearance	Data about shape, color, odor and/or taste of the product
	Weight variation	Not more than 15% from average weight
	Friability	%friability not more than 1%, no capping, laminating or other tablets breaking
	Disintegration time	Not more than 30 minutes
	Hardness	n/a
	Content of active substances or marker	90 – 110% label amount (marker) 85 – 115% label amount (chromatogram fingerprint)
Safety	Contamination of Microbial	- Aerobic bacteria not more than 5.0 x 10^3/g - Enterobacteria not more than 5.0 x 10^3/g - Yeast/Fungi not more than 5.0 x 10^3/g - *Escherichia coli* not more than 5.0 x 10/g No detection of - *Staphylococcus aureus* in 1 g - *Clostridium* spp. in 10 g - *Salmonella* spp. in 10 g
	Contamination of Heavy Metal	- Arsenic not more than 4 ppm - Cadmium not more than 0.3 ppm - Lead not more than 10 ppm

2.9.1 Appearance

Appearance of tablets is an imperative parameter. The data about appearance can be collected during the quality control process. Then, this collected data is subsequently used as a template for preferred physical appearance. The appearance must not change during the product reproduction or in stability testing process [37].

2.9.2 Weight variation

The variation of weight can indicate the content variation and the suitability of tablets development processes. This parameter is also related to physical changing during the stability process [35, 38].

2.9.3 Friability

Tablet friability means the tendency of tablet to break into smaller pieces under mechanical stress. Testing of friability can indicate the ruggedness of tablets under the stress condition such as falling from a fixed distance [37]. In this topic of testing, “capping” and “laminating” (Figure 2.5) or other tablets breaking must not occur during the test [44].

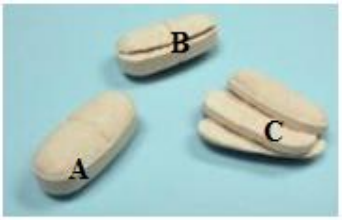

Figure 2.5: Comparative photo of complete tablet (A), capping tablet (B) and laminating tablet (C) (picture from http://www.pharmainfo.net/gate-quizzes/processing-problems-of-tablets; accessed 7 Feb 2014)

2.9.4 Disintegration

When tablet is swallowed, it must disintegrate to the original particle (powders/granules) for dissolving and absorption [37]. For herb tablets, the disintegration time must not be longer than thirty minutes [35].

2.9.5 Hardness

Tablet hardness impacts tablet’s friability and disintegration. If a tablet is too hard, it will not disintegrate in the time limit. Moreover, friability value of a tablet can be too high if it is too soft. The suitable hardness is the hardness that allows a tablet to pass the test of friability and disintegration [37].

2.9.6 Content of active substances or marker

All tablets must demonstrate that they contain the labeled active ingredients. Content of active substance or marker is a process concerning chemical determination of the active substance by using an analytical method, which is available in the monograph, research articles or self-development method [2, 37]. However, active substance in most of herbal products is still unknown. As a result, the most useful substance instead of the active substance is called "active marker", which is the main chemical compound found in the herb. In case there is no active marker available, the fingerprint of chromatogram will be carried out [35].

2.9.7 Contamination of microbial and heavy metal

Herbal product must be safe enough for consumers so it does not cause any illness. According to Thai FDA principle [43], contamination test must be carried out by the following organizations.

- Government's department of medical science or regional medical science
- Government or individual university, which provides the testing service
- Center hospital, general hospital or community hospital, which provide the testing service
- Individual laboratory, which has the accreditation
- Other laboratories, which have been approved by Thai FDA

2.10 Stability of herb tablets

2.10.1 Definition of stability

The first consideration of formulating drug or herb product is to ensure the efficacy and safety. The second is the concern whether or not the product can maintain its effectiveness from the time of manufacture to the time of use. The

study to assure the drug's maintaining is called stability test/study [38-39]. In general, the nature of everything is a constant change and this concept influences the degradation of drugs, which can be observed from their physical and chemical profile. Therefore, every product has its shelf life. In term of having a good stability profile, the product must not have any physical or chemical changes higher than 10% from the manufactured date stated on the product[38]. The factors about degradation can be described as chemical reaction. There are 2 main factors; internal factors and external factors [38-39].

1) Internal factors

Internal factors are described as the reaction of API with excipients and/or the packaging. According to the pharmaceutical technology, the word "compatibility" means the compatible of API, excipients and its packaging material without causing any interference to the API content. The incompatibility substance can be any substances that can have the reaction with API. For example, aspirin is API with acidic property. When mixed with basic property excipients (e.g. magnesium stearate), it will cause acid-based reaction and the rapid degradation . Another type of incompatibility substances is a group of substances that do not cause reaction but have an ability to blind the content of API during the process of content determination. For example, *Ganoderma lucidum* (Lingzhi mushroom) and its extract have the active marker called "total polysaccharide" if excipients, which belong to the polysaccharide group (e.g. lactose, starch, cellulose derivative), is added to formulate the dosage form, the result of content determination will be blinded by the excipients and the true polysaccharide content of API is unknown[2, 45]. The internal factors of stability can be prevented by further investigation of API and its incompatibility substances before the formulation of dosage form starts.

2) External factors

External factors (also called environmental factors) can be described as the effect of the environment on API content, which can accelerate the rate of degradation (e.g. the heat and light) and cause the reaction (e.g. oxygen and moisture)[38-39]. Appropriate packaging types can have significant impact on some but not all of these factors. For example, the package cannot provide long term protection against heat[38]. Thus, packaging selection is very important to prevent the products from these factors. Meanwhile, the unpreventable factor can be prevented by storing in the appropriate storage condition [39].

2.10.2 Stability test storage condition

For stability testing, the study consists of 3 steps; 1) before-use stability, meaning the stability before the package is opened, 2) in-use stability, meaning the stability after the package is opened, and 3) ongoing stability, meaning the stability after the product is launched in the market [46]. The test begins with storing the product in sealed packages under various conditions depending on the objectives of the tests. There are many types of stability testing, but the most widely used are long term study and accelerated study. In Thailand, the standard study is the stability testing for the product that is stored in the condition of 30^{o}C/65%RH (Relative humidity) while the accelerated study is conducted in higher-stress condition (40^{o}C/75%RH) [37, 46]. For accelerated condition, the long term storage condition must also be studied to compare the results. Shelf life of the product can be calculated from 2 means. For the long term study, the shelf life is calculated from the number of days after the product has been tested. For the accelerated type, the shelf life is calculated by quadrupling the number of days after the product has been tested. For example, if the product has passed three-month-study of accelerated study, the shelf life of product is not lower than 12 months [46-47].

2.10.3 Parameters for herb tablets stability evaluation

Thai FDA has approved the following parameters for evaluating herb tablet stability[35];

- Physical appearance
- Hardness
- Friability
- Disintegration time
- Content of marker/fingerprint of chromatogram

After each study, the result is to be compared with the data collected from day 0 of the test. In conclusion, the change of physical appearance must not be clearly observed. It must not be higher than 1% of friability testing, and must disintegrate within 30 minutes. The content of the marker and fingerprint chromatogram must not be lower than 10% and 15%, respectively [35, 46].