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PHYSICAL AND CHEMICAL PROPERTIES OF KHAMIN CHAN TABLETS: DIRECT COMPRESSION VS WET GRANULATION METHOD

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Abstract: The objective of the present study was to formulation and evaluation physical and chemical properties of Khamin chan tablets. Khamin Chan (*Curcuma longa* Linn) has been used for Thai traditional medicine. It has therapeutic properties and can be used as stomachic and carminative. Khamin Chan, commonly use in capsule formulation. Khamin Chan tablets were prepared by direct compression and wet granulation method. The prepared powders and granules were evaluated such as angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. Khamin chan tablets were evaluated for weight variation, thickness, hardness, friability, disintegration and compared curcuminoid content from each method. As a results, the contents of curcuminoids from tablet which prepared by direct compression method and wet granulation method were 6.10 and 6.25 %w/w, respectively. Wet granulation method overcomes the problems associated with moisture in excipients and can be develop to industrial scale.

Keywords: UV-Visible spectrophotometry, curcumin, curcuminiod, Khamin Chan, tablets

บทคัดย่อ: งานวิจัยนี้มีวัตถุประสงค์เพื่อพัฒนาและประเมินตำรับยาเม็ดขมิ้นชัน ทั้งทางด้านกายภาพและทางด้านเคมี ซึ่งขมิ้นชัน เป็นสมุนไพรที่ใช้ในการแพทย์แผนไทย มีสรรพคุณในการรักษาโรคกระเพาะอาหารและช่วยขับลม โดยปกติแล้วขมิ้นชันจะผลิตออกมาในรูปแบบแคปซูล การเตรียมยาเม็ดขมิ้นชัน เตรียมโดย 2 วิธี คือ การตอกตรงและการเตรียมเป็นแกรนูลเปียก นอกจากนี้ยังทำการประเมินในหัวข้อต่างๆ ได้แก่ angle of repose, bulk density, tapped density, compressibility index และ hausner's ratio โดยยาเม็ดขมิ้นชันที่เตรียมได้ จะนำมาประเมินน้ำหนักเฉลี่ย ความหนา ความแข็ง ความกร่อน และการแตกตัวของยาเม็ด อีกทั้งยังทำการศึกษาเปรียบเทียบปริมาณเคอร์คูมินอยด์ที่เตรียมได้จากแต่ละวิธี ผลการศึกษาพบว่า ปริมาณเคอร์คูมินอยด์ในยาเม็ดที่เตรียมได้จากการตอกตรงและการเตรียมเป็นแกรนูลเปียก เท่ากับ 6.10 และ 6.25% โดยน้ำหนัก ตามลำดับ ดังนั้นการเตรียมยาเม็ดขมิ้นชันโดยการเตรียมเป็นแกรนูลเปียก เป็นวิธีการที่เหมาะสม สามารถแก้ปัญหาความชื้นของผงสมุนไพรได้ดีกว่า และสามารถพัฒนาในระดับอุตสาหกรรมต่อไป

คำสำคัญ: ยูวี-วิสิเบิล สเปกโทรสโกปี, เคอร์คูมิน, เคอร์คูมินอยด์, ขมิ้นชัน, ยาเม็ด

INTRODUCTION

The powdered dry rhizome of the plant *Curcuma longa* Linn (Family Zingiberraceae), in Thai commonly called Khamin Chan. Those included in Thai Herbal pharmacopoeia1 (THP1 1995) in title Khamin Chan and Supplement to Thai Herbal pharmacopoeia 2004 (THP 2004) in title Khamin Chan Capsules. Khamin Chan is the medicinally use for treat stomachic and carminative (THP 2004). It contains a wide variety chemicals, including zingiberene, curcumenol, curcumol, eugenol, tetrahydrocurcumin, triethylcurcumin, turmerin, turmerones, and turmeronols (Almedia, 2005; Abas, 2005). The major chemical constituents are a mixture of curcumin, monodesmethoxycurcumin and bisdesmethoxycurcumin (THP 2004). In case of Khamin Chan formulation, commonly used in capsule which capsule shells were import and production cost more expensive than tablet. Therefore, the researcher is interested in developing and formulating Khamin Chan tablet which comparing preparation method (direct compression and wet granulation) and determinate of curcuminoid content by UV-Vis spectrophotometry method in formulation. This will provide a viable resolution for delivering active ingredients using a cost-effective technology.

MATERIALS AND METHODS

Materials

Curcuminoid was purchased from Fluka (USA). Medicinal plant: Khamin Chan was purchase from Vejpong pharmacy, Bangkok, Thailand. Pharmaceutical excipient: colloidal silicon dioxide, magnesium sterate, microcrystalline cellulose, sodium starch glycoate were purchased from TTK science, Bangkok, Thailand. The solvent for UV: methanol, tetrahydrofuran and water (Labscan, Thailand) were also purchased from TTK science, Bangkok, Thailand.

Evaluation of powder mixture and granules

To estimate the suitability of mixture for formulation, an evaluation that checked the physical properties of the Khamin Chan powder and excipients was required. The results of the evaluation provided data that necessary for formulation and manufacture of tablet. Evaluation of powder mixture and granules, angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio were determine using the appropriate techniques (USP33, 2009).

Angle of repose

The angle of repose of powders and granules were determined by funnel method. The 5 g of powder mixture and granule mixture was permitted to flow through the funnel freely onto the surface. The height (h) and radius (r) of powder cone was measured, angle of repose was calculated using the following equation [1]:

$$\tan \theta = h/r \quad \text{----------[1]}$$

where,

θ is angle of repose

h is height of the powder cone

r is radius of the powder cone

Bulk density

Bulk Density was determined by weighted 20 g of powder and granule mixture accurately, poured into 100 mL glass cylinder carefully without compacting. After observed initial volume, calculated using the following equation [2]:

$$\rho_{bulk} = m/V_0 \text{ ----------[2]}$$

where,
m is mass (g)
V_0 is unsettled apparent volume (mL)

Tapped density

The glass cylinder with powder mixture and granule mixture from bulk density testing was used for determine tapped density by tapped on mechanical tapped density tester (Erweka D-63150, Germany) for 1,250 strokes. After observed final tapped volume, calculated using the following equation [3]:

$$\rho_{tapped} = m/V_f \text{ ----------[3]}$$

where,
m is mass (g)
V_f is final tapped volume (mL)

Compressibility index

The compressability index of the powder mixture and granule mixture were determined by use the data from bulk density and tapped density testing, calculated using the following equation [4]:

$$\text{Compressibility index} = [(\rho_{tapped} - \rho_{bulk}) \times 100] / \rho_{tapped} \text{ ----------[4]}$$

where,
ρ_{tapped} is tapped density
ρ_{bulk} is bulk density

Hausner's Ratio

Hausner's ratio which is presented with the flow characteristics of a powder and granule mixture, calculated using the following equation [5]:

$$\text{Hausner ratio} = \rho_{tapped} / \rho_{bulk} \text{ ----------[5]}$$

where,
ρ_{tapped} is tapped density
ρ_{bulk} is bulk density

Formulation of Khamin Chan tablets

Direct compression method

Table 1. Khamin Chan formula

Ingredients	weight per tablet; mg
Khamin Chan powder	500.00
Lactose	96.35
Colloidal silicon dioxide	0.65
Magnesium stearate	3.00
Total weight (mg)	600.00

All ingredients as shown in Table 1. will be mixed and compressed by direct compression using a single punch tablet machine with a diameter of punch die set was 8 mm. Humidity in the room will be controlled to be lower than 50 %RH. Amount of drug release from tablets will be analyzed curnuminoid content by UV-Vis spectrophotometry method.

Wet granulation method

Table 2. Khamin Chan formula

Ingredients	weight per tablet; mg
Khamin Chan powder	500.00
Sodium starch glycolate	75.80
Talcum	3.00
Magnesium stearate	3.00
Tapioca starch	18.20
Water	0.61
Total weight (mg)	600.00

Wet granules will be prepared by adding 3% Tapioca starch in water into mixture of Khamin Chan powder, sodium starch glycolate, and talcum sheared by the pestle and put through a 16-mesh sieve. The granules will be tray dried at 60° using a hot air oven for 1 hour. The dried granules will then be filtered through an 18-mesh sieve. Granules will be stored in dessicators throughout the preparation. Magnesium stearate will be mixed and compressed by direct compression at using a single punch tablet machine with a diameter of punch die set was 8 mm. (all ingredients are shown in Table 2.). Humidity in the room will be controlled to be lower than 50 %RH. Amount of drug release from tablets will be analyzed curcuminoid content by UV-Vis spectrophotometry method.

Physical properties of Khamin Chan tablets

The evaluation data composed of weight variation, thickness, hardness, friability, and disintegration.

Weight variation

20 tablets were individually weighed accurately using an electronic balance and the test was performed according to official method. The Thai Herbal pharmacopoeia limit for weight variation in case of herbal tablet is not more than 10%.

Thickness

The thickness of the Khamin chan tablet was measured by using thickness tester (Erweka D-63150 Model: TBH220TD, Germany).

Hardness

For each formulation (direct compression and wet granulation) that hardness of 10 tablets was determined using hardness tester (Erweka D-63150 Model: TBH220TD, Germany).

Friability

The friability of 15 tablets (the weight of tablets for friability test is not less than 6.5 g) was determined using friability tester (K.S.L. Engineering, Thailand). The limit for friability is not more than 1%, calculated using the following equation [6]:

$$\text{Friability} = [(W_{before}-W_{after}) \times 100] / W_{before} \quad \text{----------[6]}$$

where,

W_{before} is weight of 15 tablets before test (g)

W_{after} is weight of 15 tablets after test (g)

Disintegration time (DT)

6 tablets were determined by a disintegration tester (K.S.L. Engineering, Thailand) following the official method and water was used as the medium for disintegration. The temperature of medium set at 37±0.5 °C.

Determination of curcuminoid content

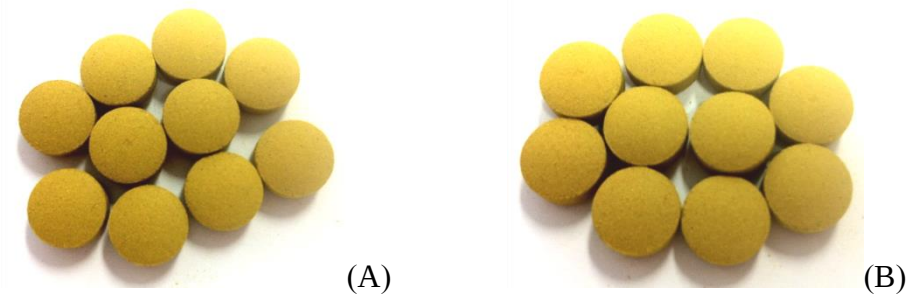
The procedure was applied from THP 2004 as followed: the standard curcumin curve was plotted at the concentrations of 0.8, 1.6, 2.0, 2.4 and 3.2 μg/mL. Prepared Khamin Chan tablets solution by weighed accurately 20 tablets and crushed with motar and pestle to obtain fine powder. Dissolved 300 mg of powder in 10 mL tetrahydrofuran and set aside at room temperature for 24 hours. Then, pipette 1.0 mL of the clear supernatant liquid was diluted with methanol up to 25.0 mL. Finally, pipette 1.0 mL solution was transferred into a 50 mL of volumetric flask. It was diluted to volume with methanol and was mixed well. To determine the stand curcumin, an absorbance of the sample preparation was measured at 420 nm, using methanol as the blank.

RESULTS AND DISCUSSION

Formulation of Khamin Chan tablets

The evaluation study and physical properties of Khamin Chan tablets prepared by direct compression method and wet granulation method were compared. Evaluation study of both preparation methods were presented a slightly different in all parameters as showed in Table 3. In case of physical properties, the physical appearance of tablets which prepared by direct compression were round shape and rough surface (found in some tablets) while tablets

which prepared by wet granulation were round shape and smooth surface as shown in Figure 1. and evaluation data of tablets as presented in Table 4. Khamin Chan tablets which prepared by direct compression method could not measure hardness because of Khamin Chan is highly volatile oil nature, Khamin Chan formulations often poses problem during production, especially sticking to the punches and physical appearance of tablets like a gum so when measure hardness, tablets was sticked to hardness tester as a result its could not measure these parameter. To enable production, wet granulation method was chosen for solve this problem. However, wet granulation process had several steps including ground, wet mixed, dry mixed and dried at 60° for 1 hour, chemical constituents may be loss from this process. The previous study suggest that the stability of curcumin is temperature dependent, it seems that partial degradation of curcumin starts at around 50°C (Siddiqui, 2015). Therefore, it was important to determined curcuminoid content to compare.



(A) (B)

Figure 1. (A) The physical appearance of tablets which prepared by direct compression and (B) wet granulation

Table 3. Data of evaluation study (n = 3)

Formulation	Direct compression	Wet granulation
Angle of repose (°)	22.93±0.02	20.81±0.01
Bulk density (g/ml)	0.50±0.11	0.34±0.04
Tapped density (g/ml)	0.59±0.01	0.43±0.01
Carr's Index (%)	15.25±0.05	20.93±0.02
Hausner's Ratio	1.18±0.05	1.26±0.02

Table 4. Data of physical properties

Physical properties	Direct compression	Wet granulation
Weight variation (mg)	598.12±0.01	596.35±0.01
Thickness (mm)	5.82±0.07	5.71±0.19
Hardness (kP)	-	2.23±0.25
Friability (%)	0.11	0.04
Disintegretion (mins)	0.50±1.30	1.27±0.04

Determination of curcuminoid content

The standard curcumin curve was plotted by preparing standard stock solution of curcumin at different concentration levels, a good linear relationship (R^2 = 0.9993) was observed between the concentrations of curcumin and the respective peak areas in the range 0.8-3.2 µg/mL. The curcuminoid content of Khamin Chan tablets prepared by direct compression method and wet granulation method were compared. The contents of curcuminoids from tablet which prepared by direct compression method and wet granulation

method were 6.10 and 6.25 %w/w, respectively as shown in Table 5.; THP 2004 officially allowable limit (not less than 5.0 %w/w). The results were presented that curcuminoid content of Khamin Chan tablets which prepared by direct compression method similar to wet granulation method. Therefore, wet granulation method is appropriate for develop in further experiment.

Table 5. Curcuminoid content of Khamin Chan tablets (n = 3)

Preparation method	Curcuminoid content (%w/w)
Direct compression	6.10±0.01
Wet granulation	6.25±0.03

CONCLUSION

Khamin Chan tablets are prepared successfully by wet granulation method. Many steps of this method not effect on curcuminoid content when compare with direct compression method. The formulation overcomes the problems associated with damp excipients like Khamin Chan powder. The analytical UV-Vis spectrophotometry method is applied from THP 2004 for determination an amount of curcuminoid. UV-Vis spectrophotometry method is a good method, due to its simplicity, rapidity and efficiency which could be employed for curcuminoid content in Khamin Chan tablet formulation.

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