Masking the Bitter Taste of Pills by Coating with a Fat Emulsion made from Irvingia malayana

Shisanupong Anukanon[1], Chaiyong Rujjanawate[2]
[1,2]School of Medicine, Mae Fah Luang University, Mueang District, Chiang Rai, THAILAND

Abstract

Krabok seed fat (from *Irvingia malayana* Oliv. ex A.W.Benn.) is a promising naturally resourced material which could be an option as a commercial fat substitute. This study formulated and evaluated the most stable emulsion containing Krabok seed fat, for coating bitter herbal pills (andrographis) in order to mask the bitter taste. The results showed that an emulsion formulation, with the required hydrophilic-lipophilic balance (HLB) of 13, exerted the most stability and was suitable for coating the bitter herbal pills. In organoleptic tests in healthy participants, it effectively masked the bitter taste. The physical evaluation of the coating layer i.e. appearance, uniformity of thickness, and uniformity of weight, was acceptable.

Keywords: ***Irvingia malayana*** **/ Pill coating / Emulsion**

Introduction

Bitterness, an unpleasant taste sensation, is commonly present in many herbal medicines, the herbs being naturally bitter tasting. Many patients are put off by this problem, leading to non-adherence and a subsequent decrease in therapeutic efficacy. Techniques for dealing with this problem have been developed. These can be divided into two main strategies, addition of sweeteners or flavoring agents (Aulton, 2002) or production of a barrier to the taste buds in the tongue (Nanda et al., 2002).

Natural waxes or fats have an extensive range of applications as raw materials for food, cosmetics and pharmaceutical production. The usage of natural fat from plants is a recent trend, to replace commercial fat materials, brought about by environmental concerns, availability and cost of those fats. This has encouraged the investigation of plants in this country as a possible source of fat. In terms of its application, natural fat can be used as a tablet coating material, to minimize the effects of bitter or unpleasant tastes in modern medicine production (Mauger et al., 1998).

Krabok seed fat (KSF) is one natural fat source that is commonly found in Thailand. This fat is derived from Krabok (*Irvingia malayana* Oliv. ex A.W.Benn., family Irvingiaceae)

(Harris, 1999), which can be found in tropical and subtropical areas such as South East Asia, South America and Africa (Phengklai, 1975). In Thailand, the Krabok wood is commonly used for charcoal, whereas the seeds are consumed as food and snacks (Bunyavejchewin et al., 2009). There are various usages of this fat: food such as cookies (Bunna et al., 2014); cosmetics such as soap and cream base (Dubois, 2008); pharmaceuticals, such as suppositories (Sirisa-ard et al., 2014). As these seeds contain large yields of fat, this is a potential way to use this fat in pharmaceutical applications, particularly as a herbal pill coating material, for taste-masking.

The objectives of this study were to formulate the most stable emulsion containing KSF, in order to mask the bitter tasting herbal pills and examine its taste-masking efficacy.

Methodology

Materials

Polyethylene glycol sorbitan monostearate (Tween 60, synthesis grade) and sorbitan monooleate (Span 80, synthesis grade) were purchased from Merck KGaA. Hexane was purchased from VWR Chemicals Limited Liability Company. Andrographis was purchased from Chaophya Abhaibhubejhr Hospital. Honey was purchased from DoiKham Company Limited.

Plant material and extraction

Krabok seeds were purchased from a local market at Mae Chan walking street, Chiang-Rai province in January 2018. After peeling the seed coat, the fat inside the seeds was dissolved in warm hexanes (about 40-45 °C) and then filtered while warm. The hexane was evaporated under reduced pressure using a vacuum rotary evaporator and the residual fat was used.

Required hydrophilic-lipophilic balance (HLB) determination of KSF

The required HLB is the amount of emulsifier required to make the most stable oil-in-water emulsion (Crowley, 2013). A series of six emulsions with HLB values ranging from 9 to 14 were prepared, by blending together the emulsifiers in different ratios (Table 1).

Table 1 Composition of different emulsions with HLB values ranging from 9 to 14

Formulation code	HLB value	Compositions			
		KSF (%w/w)	Tween 60 (%w/w)	Span 80 (%w/w)	Water (%w/w)
K1	9	10	2.22	2.78	85
K2	10	10	2.69	2.31	85
K3	11	10	3.16	1.84	85
K4	12	10	3.63	1.37	85
K5	13	10	4.20	0.90	85
K6	14	10	4.58	0.42	85

The method of preparation of emulsions was suggested by Griffin et al. (1967). 100 ml per sample, containing 10% w/w of KSF, 5% w/w blend emulsifiers (Span 80 and Tween 60) were prepared using the beaker method. The required amount of Span 80 (HLB value is 4.3) was dissolved in the KSF (oil phase) and that of the Tween 60 (HLB value is 14.9) in the distilled water (aqueous phase), separate beakers which were then heated to approximately 70°C, over a water bath. The oil phase was then added to the aqueous phase, with continuous stirring, until the emulsion reached room temperature. The required HLB of KSF was calculated using the following formula (Gadhave., 2014);

$$\text{HLB of KSF} = \frac{W_{Tween} \times HLB_{Tween} + W_{Span} \times HLA_{Span}}{W_{Tween} + W_{Span}}$$

Where: W_{Tween} and W_{Span} were the weight of Tween 60 and Span 80
HLB_{Tween} and HLB_{Span} were HLB value for Tween 60 and Span 80

The droplet size of each emulsion formulation was determined by optical microscope (Olympus CX 22 RFS1), using a calibrated ocular micrometer (Levius et al., 1953). The droplets, in groups of 300 droplets, were measured, covering at least 8 fields of view, and the average droplet diameter was calculated. The emulsion formulation with the smallest average diameter of droplet size was considered as the most stable emulsion formulation. After standing for 24 hours, all emulsion formulations were checked and droplet sizes were measured again.

Preparation of coated bitter herbal pills

The bitter medicinal plant used in this study was andrographis [*Andrographis paniculata* (Burm.f.) Nees, family Acanthaceae], the king of bitterness. The herbal pills from this plant were prepared, using refined honey to shape the andrographis powder into a pill form and these were dried in a hot-air oven at 40-50 °C for 24 hours.

The emulsion formulation, with the appropriate stability, using the above method, was prepared for coating the bitter herbal pills. Dry herbal pills were coated by dipping in the cool emulsion and dried in a hot-air oven at 40-50 °C for 24 hours (Hussein et al., 2013). The pill coating process was repeated three times. The dry coated bitter herbal pills were kept in desiccators until used.

Evaluation of coated pills

1. Physical appearances

The appearances of all coated pills were determined visually to identify their color, shape and hardness.

2. Uniformity of thickness of coating layer

The thirty uncoated-herbal pills were measured individually using a micrometer caliper. After coating, the pills were re-measured and the thickness of the coating layer was calculated using the following formula;

$$\text{Coating layer thickness} = \frac{\text{Coated pill diameter} - \text{Uncoated pill diameter}}{2}$$

3. Uniformity of weight of coating layer

The thirty uncoated-herbal pills were weighed individually. After coating, the pills were re-weighed and the weight of coating layer was calculated using the following formula;
Coating layer weight = Coated pill weight – Uncoated pill weight

Organoleptic test

The protocol of this test was approved by the Human Research Ethics Committee of Mae Fah Luang University (document no. 084/2560 dated on August 24, 2017) and each participant signed an informed consent before starting the study. Thirty participants (including both men and women) between 18 to 30 years old were enrolled.

The study was designed as a single-blind study to determine the taste-masking efficacy of the emulsion formulation containing KSF (adopted from Borodkin et al., 1991 and Nakamura et al., 2002). As the noticeable difference between the coated and uncoated pills was their visual appearance participants were blindfolded during the tasting sessions. They randomly received the bitter herbal pills (coated or uncoated pills) to hold in their mouth, then recorded the time to the perception of the bitter taste. Then, the participants spat out the pill and gargled with warm water to reset their taste sense. Twenty minutes later, they received another of the herbal pill formulations (coated or uncoated pills) and recorded the time to notice the bitter taste in the same manner.

Statistical analysis

All values were expressed as mean ± standard deviations. The data was analyzed using SPSS version 16.0 (SPSS v16.0 for Windows, SPSS Inc., Chicago, IL, USA). A *p*-value of less than 0.05 was considered to be statistically significant using Student's *t* test.

Results

Plant material and extraction

KSF from peeled Krabok seed was a white to yellowish solid with mild pungent odor. The yield of extraction was very high (90.6% yield).

Required hydrophilic-lipophilic balance (HLB) determination of KSF

KSF was used to prepare a series of six emulsions with HLB values ranging from 9 to 14. The results of the average droplet diameter of each formulation is shown in figure 1 and Table 2. The formulation with the smallest average droplet size was K5 (HLB value 13) with a diameter of 5.19 μm. It was statistically different from the other formulations, having the smallest standard variation, indicating a uniform distribution of its droplets.

Table 2 Average droplet size of KSF emulsion formulation with vary of HLB values

Formulation code	HLB value	Average droplet size (μm)	
		Initiation	After 24 hour
K1	9	17.29 ± 13.75*	Cannot measured
K2	10	12.38 ± 9.36*	Cannot measured
K3	11	13.83 ± 7.13*	Cannot measured
K4	12	11.32 ± 10.31*	Cannot measured
K5	13	5.19 ± 3.48	2.48 ± 1.15
K6	14	20.08 ± 18.94*	Cannot measured

* Significantly different from the K5 formulation, $p < 0.05$.

After standing for 24 hours, all formulations, except formulation K5, exhibited a separate layer of fat layer on top of the emulsion (data not shown), measurement of the average droplet size of these formulations therefore being not possible (environmental temperature during research was about 20-25 ℃).

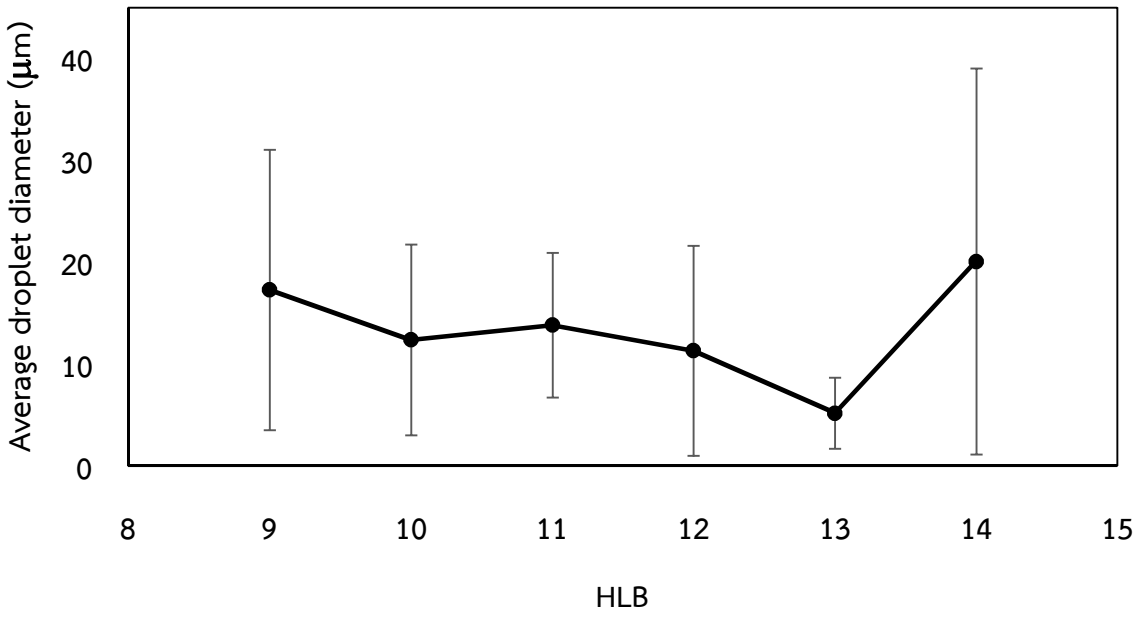

Figure 1 Curves of average droplet diameter of KSF emulsion formulations versus HLB

Preparation and evaluation of coated herbal pills

The formulation K5 was clearly the most appropriate formulation which could be used as a pill coating material in this study. The coated herbal pills were investigated to determine the various physicochemical characteristics such as appearance, uniformity of thickness and uniformity of weight. The results are shown in Table 3.

The physical visual appearance of the coated herbal pills was different from the uncoated pills. The coating was opaque in color, odorless and consistent. The average thickness and weight of the coating layer were 0.13 ± 0.02 mm and 0.06 ± 0.05 g respectively. The low standard deviation values indicated that the process used for coating process is reproducible.

Table 3 Characteristic of coating layer of herbal pills

Parameters	Coating layer of herbal pills
Physical appearance	Opaque in color, odorless and dry
Coating layer thickness (mm)	0.13 ± 0.02
Coating layer weight variation (g)	0.06 ± 0.05

Organoleptic test

The study enrolled 30 participants (2 man, 28 women) with a mean age of 20.4 ± 1.4 years old. After holding the pills in the mouth, the mean time to bitter taste of the uncoated pills was less than 10 seconds (8.40 ± 6.80 seconds), whereas the mean time to bitter taste of the coated pills was 26.89 ± 21.95 seconds, statistically different from the uncoated pills (p value < 0.05).

Discussion and conclusion

The required HLB values of a fat are indicated by the composition of their fatty acids (ICI Americas Inc., 1984). There are several previous studies that determined the composition of KSF. It is rich in saturated fatty acids lauric acid (C12:0) and myristic acid (C13:0), in the ranges of 42-47% and 41-42% respectively (Bandelier et al., 2002 and Sonwai et al., 2012). This finding showed that the required HLB values for the most stable emulsion of KSF was determined as being approximately 13. This contradicts indirectly the research of Sonwai et al. (2012) which suggested that KSF had a lauric acid content within the range of coconut and palm kernel oils, which both have an HLB of about 8.

In general, the stability of oil-in-water emulsions is dependent on environmental temperature (Crowley, 2013). The emulsions can separate into 2 phases; an oil-in-water

emulsion phase and an excess fat phase at low temperatures (Forgiarini et al., 2001). This was supported by our study which showed that unstable emulsion formulations were separated into 2 layers after standing for 24 hours. Because of the lower melting point of KSF, compared to other saturated fats (approximately 38-39 °C; Sonwai et al., 2012), it may easily be solid at low temperatures, which is an interesting way to monitor the stability of the emulsion from KSF.

After the pill coating process, the physical properties of coated pills i.e. physical appearance, uniformity of thickness, and weight were acceptable, with low standard deviation values, which indicated that the process of preparation is reproducible.

The bitterness perception in thirty participants demonstrated that the time to experience the bitter taste of the coated pills, when holding within the mouth, was delayed sufficiently to allow swallow without a bitter taste perception. Because of their water-insoluble properties, they can reduce drug solubility in saliva and produce a barrier between the drug and the taste buds (Bettman et al., 1998). Moreover, KSF also can partially melt at body temperature (Sonwai et al., 2012) which should not affect drug absorption during passage through the stomach.

This study suggests that KSF can effectively mask the bitterness of herbal pills, hopefully this material can be used as an alternative fat substitute in the future.

Acknowledgments

This study was financially supported by Mae Fah Luang University, Chiang Rai, Thailand. English language support was kindly provided by Dr. Roger Callaghan, School of Medicine, Mae Fah Luang University.

References

Aulton, M. E. (2002). **Pharmaceutics: the science of dosage form design** (2nd ed.) New York: Churchill Livingstone.

Bandelier, J., Chunhieng, T., Olle, M., Montet, D. (2002). Original study of the biochemical and oil composition of the cambodia nut *Irvingia malayana*. **J Agric Food Chem**. 50(6), 1478-1482.

Bettman, M. J., Percel, P. J., Powell, T. C. (1998) **Effervescent microcapsules.** US Patent No. 5,709,886.

Borodkin, S., Sundberg, D. (1991). Polycarboxylic acid ion exchange resin, adsorbates of taste coverage in chewable tablets. **J Pharm Sci**. 60, 1523-1527.

Bunna, P., Sahaspot, S., Khuikhoen, W., Thedkwanchai, S. (2014). **Malekcaboke cookies**. Research report. Retrieved February 11, 2018, from https://repository.rmutp.ac.th/bitstream/handle/123456789/1267/HEC_56_32.pdf?sequence=1&isAllowed=y.

Bunyavejchewin, S., Davies, S. J., Ashton, P. S. (2009). **Forest trees of Huai Kha Khaeng wildlife sanctuary, Thailand**. Bangkok: National Parks, Wildlife and Plant Conservation Dept.

Dubois, V. (2008). Reverse vesicle containing a hydrophobic phase. European Patent No. EP1905425 A1.

Forgiarini, A., Esquena, J., González, C., Solans, C. (2001). Formation and stability of nano-emulsions in mixed nonionic surfactant systems. **Progr Colloid Polym Sci**. 118, 184-189.

Gadhave, A. (2014). Determination of hydrophilic- lipophilic balance value. **Int J Sci Res**. 3(4), 573-575.

Griffin, W. C., Lynch, M. J., Lathrop, L. B. (1967). Emulsions, part one. **Drug Cosmet Ind**. 101(4), 41.

Harris, D. J. (1999). **Irvingiaceae-species plantarum-flora of the world part I**. Canberra: Australian Biological Study.

Hussein, A. A., Ghareeb, M. M., Hussain, R. A. A. (2013). Preparation and characterization of meloxicam colon targeted coated tablets. **Int J Pharm Pharm Sci**. 5(1), 338-342.

ICI Americas Inc. (1994). **The HLB system, a time-saving guide to emulsifier selection**. New York: ICI Americas Inc.

Levius, H. P., Drommond, F. G. (1953). Elevated temperature as an artificial breakdown stress in the evaluation of emulsion stability. **J Pharm Pharmacol**. 5, 743-756.

Mauger, J. W., Robinson, D. H. (1998). **Coating technology for taste masking orally administered bitter drugs.** U.S.Patent No.5,728,403.

Nakamura, T., Tanigake, A., Miyanaga, Y., Ogawa, T., Akiyoshi, T., Matsuyama, K. (2002). The effect of various substances on the suppression of the bitterness of quinine–human gustatory sensation, binding, and taste sensor studies. **Chem Pharm Bull**. 50, 1589-1593.

Nanda, A., Kandarapu, R., Garg, S. (2002). An update on taste masking technologies for oral pharmaceuticals. **Indian J Pharm Sci**. 64(1), 10-17.

Phengklai, C. (1975). Studies in flora of Thailand: Hippocastanaceae, Cannabitaceae, Irvingiaceae, Casuarinaceae. **Thai For Bull (Bot)**. 9, 1-11.

Sirisa-ard, P., Piyamongkol, S., Charumanee , S., Yotsawimonwat, S., Pholsongkram, K. (2014). Development of krabok (*Irvingia malayana*) wax as a suppository base. **Acta Hortic**. 1023, 71-76.

Sonwai, S., Ponprachanuvut, P. (2012). Characterization of physicochemical and thermal properties and crystallization behavior of krabok (*Irvingia malayana*) and rambutan seed fats. **J Oleo Sci**. 61(12), 671-679.