Influence of Diluents and Binders on the Yield, Friability, and Flowability of *Alpinia galanga* Extract Granules

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ABSTRACT

A public increasingly wary of the use of antibiotic growth promoters in animal husbandry, and growing bans on their use, has led to an increased interest in alternative means of drug replacement using plant extracts. Alpinia galanga extract is one such alternative because of its several beneficial effects for promoting animal growth. However, A. galanga extracts prepared from maceration of the plant rhizomes are sticky, semisolid, unable to flow, and difficult to mix with other feed substances. These physical characteristics, as well as its pungent odor, make it difficult to use the extract "as is" as a feed supplement. This study aims to examine the potential of certain diluents and binders commonly used as excipients in granule preparation for improving the characteristics–yield, friability, and flowability–of the A. galanga extract.

The results showed that the type and concentration of diluent and binder affected the friability and flowability as well as yield of the A. galanga extract granules. Of the three diluents used in this study, tapioca was found to be the most suitable diluent for producing A. galanga extract granules. The use of a binder in granule production, particularly starch paste, decreased granule friability and increased the yield. Furthermore, using a combination binder ñ starch paste with either polyvinyl pyrrolidone or gelatin, significantly increased the desirable characteristics of the granules over the single binder. Starch paste and polyvinyl pyrrolidone potentiated A. galangal extract granules with the highest flowability, whereas starch paste and gelatin provided the granules with the least friability and the highest yield.

Keywords: Alpinia galanga, Plant extract, Granule, Diluent, Binder

INTRODUCTION

Alpinia galanga (Zingiberaceae) is an indigenous medicinal plant found in the tropics, particularly in China, India, Thailand, and other Southeast Asian countries. The rhizomes of this plant are used extensively for flavoring food and as traditional medicine for various ailments. In China and Thailand, it is used as a folk medicine for stomach health. This plant is used also as an antiseptic and

antibacterial agent and described as a carminative and digestive stimulant (Fransworth and Bunyaprapraphatsara, 1992; Yang and Eilerman, 1999). In India, it is a reputed drug in indigenous systems of medicine and used in southern India as a domestic remedy. In Malaysia, the rhizomes are used for the treatment of cough, asthma bronchitis, headache, inflammation, rheumatoid arthritis, and colic (Burkill, 1966). In 2003, Matsuda et al. (2003a, 2003b) categorized this plant as an antimicrobial, carminative, stomachic, anti-rheumatic, anti-flatulent, and anti-itching agent. Its anti-rheumatic action resulted in suppression of synthesis of prostaglandin through inhibition of cyclooxygenase-1 and cyclooxygenase-2 (Grzanna et al., 2005). Janssen and Scheffer (1985) reported that the monoterpenes in the essential oil from the fresh rhizomes of the plant contains an antimicrobial activity against *Trichophyton mentagrophytes*. The ethanol crude extract of *A. galanga* has an inhibitory effect against *Staphylococcus aureus* (Oonmetta-aree et al., 2006). In addition, this plant is reported to offer antioxidant properties (Habsah et al., 2000; Mayachiew and Devahastin, 2008). The aqueous acetone extract from rhizomes of this plant has an inhibitory effect on lipopolysaccharide (LPS)-induced nitric oxide production (Morikawa et al., 2005).

Antibiotics at sub-therapeutic or nutritional levels have been intensively used for decades as feed additives in pig production in order to improve growth rates of the animals (Cromwell, 2002). Even though their mode of action is not fully understood, there is evidence that nutritional antibiotics work in part by decreasing the overall numbers and/or specific bacterial species or their metabolic activities in the gastrointestinal tract (Visek, 1978; Anderson et al., 1999; Gaskins et al., 2002; Dibner and Richards, 2005; Page, 2006). It was reported that growth promotion by in-feed antibiotics is related and proportional to the inhibition of the total microbial load and microbial metabolism in the stomach and the jejunum (Dierick et al., 2002a). A reduction in the general bacterial growth in the small intestine and pathogen proliferation should be major targets to improve animal performance and/or health (Apajalahti and Kettunen, 2006). However, since January 2006, by regulation (EC/1831/2003), the EU has banned the use of in-feed antibiotics. For this reason, as well as public concern, reliable alternatives are needed to replace in-feed antibiotics. Herbs, spices, plant extracts, and derived products have been increasingly proposed and reviewed as alternatives for in-feed antibiotics for promoting pig growth (Doyle, 2001; Kamel, 2001; Turner et al., 2001; Lee et al., 2004; Westendarp, 2005). Different modes of action such as antioxidant, antimicrobial, coccidiostatic, anti-inflammatory, immunomodulating effects, and endogenous enzyme secretion enhancement are described, depending on the product considered. Many crude extracts and essential oils of herbal origin, well known for their antimicrobial properties (Cowan, 1999; Nychas and Skandamis, 2003; Burt, 2004), offer promise.

A. galanga extract shows considerable promise as a natural growth promoter for animals, given its edible safety and various potential beneficial effects mentioned above. However, the outer appearance and strong pungent odor of the extract might cause difficulty for animals to take orally. In addition, its characteristic sticky mass can retard feed homogeneity during the mixing process. In

order to mask these disadvantages of *A. galanga* extract, a suitable dosage form needs to be designed. Granule is a dosage form that enhances the flowability of powder (Rowe, 1990). Hence, it is suitable as an animal feed premix additive since it is easier than powder to mix with principle animal feed powders. Granules are also better at covering/masking any undesirable tastes and/or odors of active ingredients. However, in the development of desirable granules, many processing parameters including pharmaceutical excipients such as the type and concentration of diluent and binder used need to be controlled for to provide the most suitable individual granule characteristics for feed additives. The friability of granules is one of the most important granule characteristics. High quality granules, the most physically stable in size and shape during handling or transport, are those that are the least friable. The rheology or flowability of granules is also important for animal feed additives. The highest quality additives, those with high flowability, are those that can be easily and efficiently mixed with the principal animal feeds. This study reports the effect of two types of pharmaceutical excipients, diluents and binders, on the friability and flowability of *A. galanga* extract granules.

MATERIALS AND METHODS

Materials

For plant material, this study used the rhizomes of *A. galanga*, aged 10-12 months and cultured in northern Thailand. A voucher specimen of the plant was deposited at the Herbarium of the Faculty of Pharmacy, Chiang Mai University, Thailand.

For granule excipients, this study used food-grade tapioca starch, rice starch, and glutinous starch as diluents, all sourced from Thailand. For binders, this study used corn starch, polyvinylpiloridone K90, and gelatin, all sourced from Fluka, Switzerland.

Preparation of the crude extracts

Fresh rhizomes of *A. galanga* were sliced into small pieces and dried at 50°C for 48 h then ground into a fine powder. The obtained dried powder was macerated in a 95% ethanol solution for four cycles at room temperature. Each cycle lasted three days, with 1 h mechanical stirring everyday. The filtrates from each macerated cycle were pooled together. The solvent was removed under reduced pressure at 45°C using a rotary evaporator. The resultant extract was stored at 4°C until use.

Method of granulation

Wet granulation was used to prepare the granules of *A. galanga* extract. All granule excipients were dried at 60°C for 5 h and sieved manually through 150 µm opening sieve mesh before use. The extract and excipients for each formula, with weight ratios of 1:1, 1:1.25, 1:1.5, 1:1.75, and 1:2, were mixed thoroughly using mortar and pestle. For binders in granule form, the diluent was added first to the extract and mixed well before adding the binder solution or paste. The

solid wet mass obtained was then pressed through an 8 mesh sieve. The resultant wet granules were dried at 60°C for 24 h. All operating conditions were selected based on several preliminary tests. After the drying process was completed, the granules were sieved through 12 mesh and received by 14 mesh sieves using a sieve apparatus (Retch, model AS 200 Basic, Haan, Germany). The granules that passed through the 12 mesh sieve and were retained by the 14 mesh sieve were collected and used for further study.

Friability test

The friability of the granules was determined using the method, with some modification, described by Oulahna et al. (2003). A friability tester with a standard rolling-drum apparatus (Pharma Test, Hainburg, Germany) was used. The granules of *A. galanga* extract prepared by the above method were left at room temperature for 24 h in the desiccator with silica gel. The granules with exact weight (Wo) were subjected to friability measurement. After 200 drum rotations, the granules were sieved through the 14 mesh sieve. The weight of the granules retained on the sieve (Wt) was determined. The friability of the granules was calculated using the following equation:

$$\text{Friability (\%)} = \frac{\text{Wo - Wt}}{\text{Wo}} \text{ X } 100$$

Flowability test

The flowability of the granules was evaluated using two different parameters; the repose angle and the compressibility ratio or Carr index. The repose angle (θ) of the granules was measured using a glass funnel and graph paper. The distance between funnel and graph paper was set to 10 cm (h). An amount of 10 gm of granules was allowed to flow through the funnel onto the graph paper. The reading of the radius (r) at the base of the cone formed by the granules on the graph paper was recorded. Tan θ was determined by h/r. The repose angle was calculated from arc tan θ.

The Carr index of the granules was calculated according to the following equation, where Dt and Db are the tapped density and bulk density of the granules, respectively:

$$\text{Carr index} = \frac{\text{Dt - Db}}{\text{Dt}} \text{ X } 100$$

The density of the granules was determined by filling the sample material into a tarred graduated cylinder to the 100-ml mark. The bulk density was calculated as the ratio of the sample weight to the sample volume. The cylinder was then tapped until constant volume was achieved using a Jolting volumeter (Meditron Co, Ltd., Thailand) and the tapped density was calculated as the ratio of the sample weight and the resultant constant volume.

Statistical analysis

Statistical significance was evaluated using ANOVA. The differences were considered significant when the p-value < 0.05.

RESULTS AND DISCUSSION

The yield and physical characteristics of the extract

The extract of *A. galanga* was obtained after solvent evaporation of the ethanolic macerated filtrate of the rhizome. The yield of the extract was 22.8 ± 0.5% w/w based on the dried rhizome powder. The extract was a sticky viscous-liquid mass with dark brown color (Fig. 1) and a strong pungent odor of *A. galanga.* The extract was checked for its antimicrobial activity before use (data not shown).

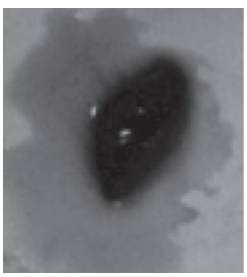


Figure 1. The outer appearance of *A. galanga* extract.

Effect of diluent on the physical appearance of the extract and granules

Diluents have been reported to play important roles on the characteristics of dosages delivered in solid form (Ford et al., 1987; Holgado et al., 1995). This study looks at the effect of a variety of diluents for preparing *A. galanga* extract, with the purpose of identifying the most suitable type and concentration. Tapioca starch, rice starch, and glutinous starch were used individually as a diluent to form granules of *A. galanga* extract. Several ratios of extract to diluent were studied. The diluents varied in their efficiency of yielding a mixture with good characteristics in a semisolid mass form suitable for granulation. Granules could not be produced if the mixture obtained was either too liquefied (a liquid sticky mass) or too solidified (a powdery semisolid or solid mass). A variety of concentrations for each diluent (Table 1) were tested. The most suitable ratio of extract to starch was 1:2 for tapioca starch, 1:1.5 for rice starch, and 1:2 for glutinous starch.

Table 1. Physical characteristics of *A. galanga* extract-diluent mixtures.

Ratio of extract to diluent	Diluents		
	Tapioca starch	**Rice starch**	**Glutinous starch**
1:1.00	Liquid sticky mass	Liquid sticky mass	Liquid sticky mass
1:1.25	Liquid sticky mass	Semisolid sticky mass	Liquid sticky mass
1:1.50	Liquid sticky mass	Semisolid mass	Semisolid sticky mass
1:1.75	Semisolid sticky mass	Semisolid powdery mass	Semisolid mass
1:2.00	Semisolid mass	Solid powdery mass	Semisolid powdery mass

These mixtures were selected for further granulation. For granule preparation, a solution of polyvinyl pyrrolidone (PVP) in isopropyl alcohol was used as a binder. A binder solution containing 0.8 gm PVP was added to 50 gm mixtures of the extract and diluent. The yield of the granules was determined and the granule friability was evaluated. The results are shown in Figure 2. The results demonstrated that the granules obtained from each diluent were significantly different in terms of yield and friability ($p<0.05$). The granules produced using tapioca starch had the highest yield of 62.9±0.4%, about two times higher than those with rice starch and glutinous starch. Okonogi et al. (2010) studied the internal structure of several starches available in Thailand and reported that tapioca starch, rice starch, and glutinous starch possessed different internal crystalline structures. Each starch contains amylose and amylopectin in different ratios (Klanarong et al., 2003). The internal structure and composition differences of the three starches used in this study were the major factors causing the friability differences of the granules produced. The granules produced using tapioca starch diluent exhibited the least friability, less than that produced from glutinous starch and rice starch. From the results of this study, tapioca starch is the most suitable diluent for producing *A. galanga* extract granules. It results in granules with both the highest yield and lowest friability.

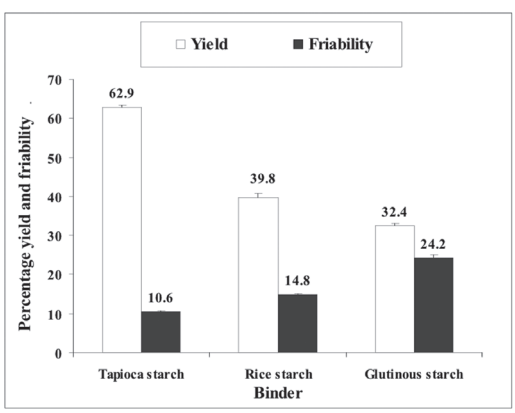


Figure 2. Effect of diluents on the yield and friability of *A. galanga* extract granules.

Effect of binder on the physical appearance of the extract and granules

As the previous results revealed, tapioca was the most suitable diluent for preparing granules of *A. galanga* extract. However, even though the friability of the granules was the lowest of the three diluents studied, it was inadequate for producing granules of standard strength. The choice of binder is one of the most important factors influencing granule properties (Zuurman et al., 1995). The binder can decrease granule friability as well as increase its strength. The best binder yields granules with the least friability.

To select the most suitable binder, this study first evaluated the effects of different binders individually on the characteristics of the *A. galanga* extract granules produced from tapioca diluent. Three binders were selected for study: polyvinyl pyrrolidone (PVP), gelatin, and starch paste. The results are shown in Fig. 3. Of the three binders used individually, starch paste showed the highest potential as a binding agent for *A. galanga* extract granules. It produced granules with the highest yield (67.5±0.6%) and least friability (5.3±0.8%). Therefore, starch paste was selected for further study.

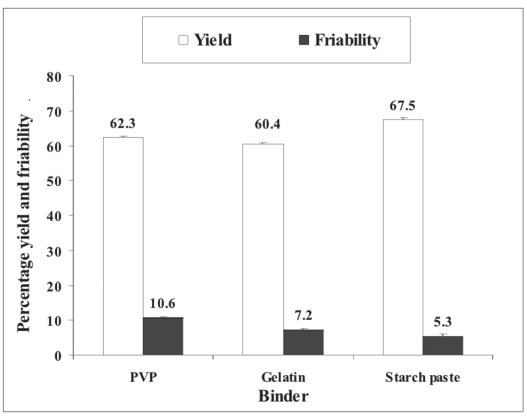


Figure 3. Effect of binders on the yield and friability of *A. galanga* extract granules.

As the use of mixed binder combinations has been reported to yield desirable products (Zhou et al., 1996), this study then looked at using starch paste in combination with other binders. The effects of binder combinations of starch paste with PVP (S-P) and starch paste with gelatin (S-G) on *A. galanga* extract granules was evaluated. As before, the granules were prepared with tapioca as the diluent. The amount of each binder mixture solution used depended on the desirable semisolid mass obtained, however, they were all in a similar range of 8-10%. The yield and friability results of the granules obtained are shown in Figure 4. The yield of the granules obtained from the mixed binder significantly increased ($p<0.05$) to 81.3% for the S-P mixture and 86.9% for the S-G mixture. In addition, the friability of the granules decreased significantly ($p<0.05$) to approximately 1.6% for the S-P mixture and 1.2% for the S-G mixture. Granule friability is dependent on binder-substrate adhesion and binder cohesion (Rowe,

1990). The results of the present study show that a mixed rather than single binder produced less friable granules. In addition, granules produced using the S-G binder mixture showed higher yield and less friability than those using the S-P mixture.

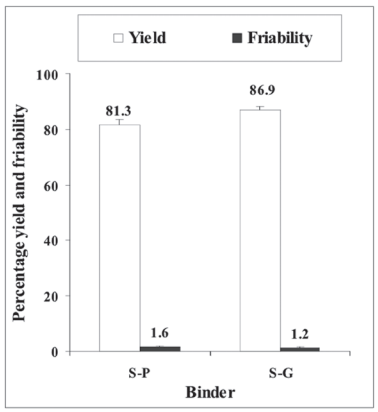


Figure 4. Effect of binder combinations on the yield and friability of *A. galanga* extract granules.

Granules from both binder mixtures were then investigated for their flowability. The repose angle and Carr index of the granules using the S-P binder mixture was significantly lower than those using S-G as shown in Fig. 5. These results demonstrate the influence of the binder on *A. galanga* extract granules. The combination binder yielded granules with better characteristics than those produced using the single binder. The S-P binder resulted in granules with almost two times higher flowability than the S-G binder.

From these results, both S-P and S-G increased the desirable properties of *A. galanga* extract, however, in different ways and extents. S-G had a slight advantage over S-P in yield and friability of granules whereas S-P had a significant advantage over S-G in granule flowability.

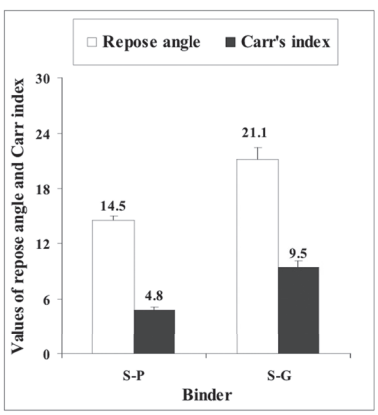
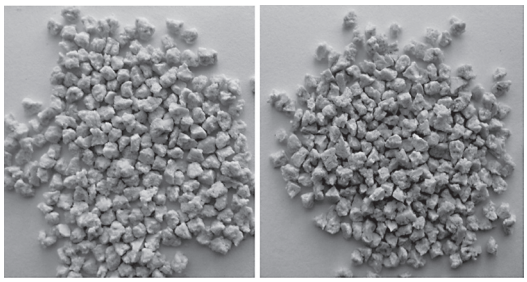


Figure 5. Effect of binder combinations on rheology of *A. galanga* extract granules.

The outer appearance of *A. galanga* extract granules obtained from this study is shown in Fig. 6. The produced granules covered or masked the disadvantageous color of the extract.



(A) (B)

Figure 6. The outer appearance of the A. galanga extract granules obtained using mixtures of starch paste-polyvinyl pyrrolidone (A) and starch paste-gelatin (B) as binders.

CONCLUSION

The present study has demonstrated the influence of two types of pharmaceutical excipients–the diluent and the binder–on granules of *A. galanga* extract. The results showed that the type and concentration of both pharmaceutical excipients affected granule characteristics, including their yield, friability, and rheology. *A. galanga* extract on its own was a sticky semisolid that with its inability to flow was difficult to mix with other feed substances. The granules developed in the present study showed the potential to mask these disadvantageous properties of the extract. Among the three diluents studied, tapioca was the most suitable diluent for producing useable *A. galanga* extract granules. In turn, different binders affected the yield and friability of the *A. galanga* extracts granules produced using tapioca starch. Using binders had the positive effect of decreasing granule friability, with starch paste showing the most benefit when used individually. Combining binders, starch paste with either polyvinyl pyrrolidone or gelatin, significantly increased the desirable characteristics of the granules even further.

This study has found that *A. galanga* extract granules produced using a diluent of tapioca starch in a 1:2 extract with a combination binder of either starch paste-polyvinyl pyrrolidone or starch paste-gelatin offers the most desirable yield, friability, and flowability characteristics for use as a feed supplement.

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