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Formulation of Enteric Coated Tablets Containing Pineapple (*Ananas comosus* Merr.) Fruit Juice

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Abstract
Pineapple fruit has been empirically used as an anthelmintic. One obstacle of the usage of pineapple as an anthelmintic is that its chemical content can increase the incidence of gastric mucous membrane irritation. To overcome this problem, an enteric-coated tablet dosage form was selected, which can prevent the dissolution of tablet in the gastric fluid but it can dissolve in an alkaline medium. Thus it can eradicate the worms that live in the intestine. A study on the formulation of enteric coated tablet containing pineapple fruit juice has been carried out. Pineapple juice was obtained by using a juicer. Tablets were prepared by wet granulation method.The physical quality of resulting granules was evaluated including moisture content, repose angle, flow rate, and compressibility. Granules were then compressed to yield tablets of 300 mg, in which each tablet contains 71.5 mg of pineapple fruit extract. The quality of resulting tablets was evaluated including friability, hardness, weight uniformities, and disintegration time. One formula of tablet was prepared and then coated using a coating solution of Eudragit L-100 with the additional weights of 3%, 4%, and 5%. The quality of resulting enteric coated tablets was evaluated including additional weight uniformities, hardness, disintegration time, and physical appearance of tablet. The stability testing of contents was performed using TLC. Physical appearance data were analyzed using chi square. It can be concluded that pineapple fruit juice could be formulated as an enteric coated tablet with the additional weight of 4%.
Keywords: coated tablet; Eudragit L-100; pineapple fruit.

Background

Worm infection is one of the emerging diseases due to the poor condition of sanitation and hygiene. Worm is a parasite that lives in the body, leading to the retardation of physical and intellectual development of children. The symptoms of patient are as follows: weak physical condition, big tummy, skinny although polyphagia, no appetite. Based on diagnostic laboratory results, worm infection is characterized by the presence of egg worms in the feces, sputum, urine or finger of patients (Sukarban & Santosa, 1995).

The following synthetic medicines can be administered to treat worm infection including: levamizol, diethyl carbamazine, thiamizole and pyrantel pamoate (Sukarban & Santosa, 1995). In general, synthetic drugs are relatively expensive and frequently elicit unwanted side effects such as nausea, vomiting, dizziness and allergic reactions. As a subsitute to the synthetic drugs, traditional medicines with relatively low side effects could be employed. The following plants are efficacious for worm infection: pineapple *(Ananas commusus* Merr.), papaya *(Carica papaya* L.), *bangle* rhizome *(Zingiber purpurea* Roxb), *temu giring (Curcuma heyneona* Val.), *temu hitam (Curcuma aeruginosa* Roxb.) and *pinang (Areca catechu* L.) (Anonymous, 1989).

Considering the availability, relatively low cost, pleasant taste enabling its use for children, pineapple fruit *(Ananas commusus* Merr) was selected in this study. The chemical constituents in pineapple, among others, are: bromelin enzyme, saponins, flavonoids, polyphenols, vitamin C, organic acids, dextrose and saccharose (Anonymous, 1989). Bromelin enzyme is allegedly effective as an anthelmintic as this proteolytic enzyme could cleave the proteins in the tissue. This will in turn soften and weaken the body of worm. Pineapple extract at a concentration of 12% w/v demonstrates anthelmintic effect, similar to 3.5% w/v piperazine citrate (Wulandari, 2004).

One obstacle of the usage of pineapple as an anthelmintic is that its chemical content can increase the incidence of gastric mucous membrane irritation. To overcome this problem, an enteric-coated tablet dosage form was selected. This dosage form was selected because it has many advantages such as: relatively small volume with large amount of active ingredients, solid shape resulting in an easier packaging, storage and transportation, and physico-chemically more stable than liquid dosage form. The presence of an enteric coated film which is not soluble in gastric acid is expected to reduce the irritation of mucous membrane. This film dissolves in alkaline medium of small intestine, resulting in the eradication of parasitic worms in the intestine. In addition, enteric-coated tablet dosage form may improve the appearance of drug preparation (Allen *et al.*, 2011).

The widely used enteric coated films include: celulose acetate phthalate (CAP), Eudragit L, Eudragit S, HPMCP and polyvinyl acetate phthalate. Eudragit L was selected in this study because this film is resistant to gastric acid and soluble in intestinal fluid at pH 6. It is also stable during storage and water medium can be used as a solvent to prepare a coating solution. The spraying time of this coating solution is shorter, the coating solution has a low viscosity and is relatively low cost. The usual concentration of Eudragit L-100 is 3-6% (Agoes, 1984; Rowe *et al.*, 2009).

Material and Mehods

Materials and Equipments

Pineapple *(Ananas commusus* Merr) was collected from the plantation in Kediri, East Java. Prior to the study, the determination of plant material was conducted by the Indonesian Institute of Sciences (LIPI) Purwodadi Botanical Garden, Pasuruan-East Java. Other materials of pharmaceutical grade included aerosil, dibasic calcium phosphate, Ac-Di-Sol, magnesium stearate, talcum, PVP K-30, ethanol, acetone, PEG 400, and Eudragit L-100.

Equipments used in this study were oven, moisture analyzer (Sartorius MA 30 type, Germany), analytical balance (Toledo Metler AL 204 type, Germany), single punch tabletting machine, tablet hardness tester (Schleuniger 6D-30 type, Germany), tablet friability tester (Erweka TA-3 type, Germany), disintegration apparatus (Erweka ZT 3-1 type, Germany), glass apparatus and other supporting equipments.

Preparation of Crude Material

Pineapple fruit employed in this study was a fresh, ripe and yellow, no rotten and free from pests and diseases. The fruit was peeled and the core of pineapple fruit was removed, to obtain the fruit flesh only and then was washed thoroughly.

Preparation of extract powder

One kilogram of pineapple flesh was cut into small pieces, crushed in a blender to obtain a slurry mass, then was squeezed using a flannel cloth to obtain a pineapple fruit juice. The juice was heated in a water bath at a controlled temperature not more than 50 °C to yield a viscous extract. Aerosol was added at a ratio of 1:0.75 considering the resulting dry extract of 10%, was poured into a tray and dried in an oven at a temperature of 50 °C, to obtain a dry extract. The resulting extract was weighed, finely grounded and sieved through a-40 mesh siever to obtain a dry extract ready to be used for tablet manufacturing process.

Dose Calculations

Based on Wulandari (2004), 12 g of dry extract is equivalent to 3.5 g of piperazine citrate. The dose of piperazine citrate in the market was 500 mg.

Dose of anthelmintics in the dry extract:

(12 g / 3.5 g) × 500 mg = 1.714 g dry extract / day

In this study, each tablet contained dry extract of pineapple fruit juice 71.5 mg and eight tablets were administered three times daily.

Tablet Formula

The core tablets of pineapple fruit juice was prepared by wet granulation method in one formula replicate. It contained 71.5 mg of dry extract as shown in Table 1. Core tablets of good quality were coated with Eudragit L-100 coating solution at a concentration of 4% as shown in Table 2.

Table 1. The formula of tablets

Name of materials	Function	Weight of one tablet (mg)	One batch (g)
Pineapple dry extract	Active ingredient	71.5	92.95
Aerosil	Desiccant	71.5	92.95
Dibasic calcium phosphate	Filler	124	161.20
Ac-Di-Sol (4%)	Disintegran	12	15.6
Magnesium stearate (1%)	Lubricant	3	3.9
Talcum (3%)	Glidant	9	11.7
PVP K-30 (3%)	Binder	9	11.7
	Total weight	300	390

Table 2. The formula of coating

Materials	Weight (g)
Eudragit L-100	4
PEG 400	0.4
Ethanol: acetone = 60: 40	to 100 mL

Tablet Manufacturing Process

The dry extract of pineapple fruit juice of 185.9 g was mixed with 161.20 g of dibasic calcium phosphate, 15.6 g of Ac-Di-Sol and 11.7 g of PVP K-30 until homogeneous. Water was then added to form a granulate mass and subsequently sieved through a-16 mesh siever. Granules were dried in an oven at a temperature of 50 °C for 8 hours and were re-sieved through a-20 mesh siever. The resulting granules were weighed. Granules were mixed with 3% of talcum and 1% of magnesium stearate, and their physical quality was evaluated including: moisture content, compressibility, flowability and repose angle. Granules of good quality were compressed using a single punch tabletting machine with a-10 mm diameter of mold and a tablet weight of 300 mg. The quality of resulting tablets was evaluated including: weight uniformity, hardness, friability and disintegration time. Core tablets of good quality were coated with Eudragit L-100 coating solution at a concentration of 4% to weight coating layer 3% (FA), 4% (FB) and 5% (FC). The quality of resulting coated tablets was evaluated including: weight of coating layer uniformities, hardness, disintegration time and visual inspection on the surface of coated tablets.

Characteristic quality of granules

Moisture content (% MC)

Granules as much as 1-2 g were evaluated using a moisture analyzer at 100 °C until a constant weight. The quality standard moisture content of 2 -5% (Bandelin & Shangraw, 1989; Voigt, 1995).

Flow time and repose angle

Determination of flow properties of granules with Cartensen method using 100 grams of powder granules. Determination of flow properties of granules made using the parameters of time and repose angle. The quality standard flow time of less than 10 seconds (Voigt, 1995) and repose angle 25-40° (Marshall, 1996).

Compressibility

Compressibility is the percentage ratio between the difference in tapped density and bulk density. The quality standard compresibility of 5-18% (Fierse & Hagen, 1996).

Characteristic physical quality of tablet

Weight uniformity

Uniformity of weight carried by weighing 20 tablets, then calculated the average weight of each tablet. Not more than 2 tablets deviate more than 5% and not one tablet deviate more than 10% (Anonymous, 1979).

Hardness

The test was done using 10 tablets. The quality standard hardness of 4-8 kgf (Parrot, 1971).

Friability

The test was done at 25 rpm for 4 min using 20 tablets. The quality standard friability of less than 1% (Banker & Anderson, 1996).

Disintegration time

Disintegration time test using 6 tablets. Tablet core: use water as a medium of disintegration at temperature 37±2 °C, the quality standard disintegration time of no more than 15 minutes (Anonymous, 1979). Enteric coated tablet: used artificial gastric fluid as a disintegration media at temperature 37± 2 °C and equipments run for 2 hours, tablets should not be broken, cracked or become soft. After that replace artificial intestinal fluid LP temperature 37±2 °C as a disintegration media for a period of 1 hour with the time limit specified in each monograph all which is tablets should be crushed all (Anonymous, 1995).

Visual inspection on coated tablet

Visual inspection on the surface of coated tablets made by taking 100 tablets at random in each formula and then observed by 10 panelists using the following criteria: + (rough surface), + + (rather rough surface) and + + + (smooth surface).

Data analysis

Physical quality tablet include weight, hardness and disintegration time using one way ANOVA ($p < 0.05$) and a visual test using the chi-square ($p < 0.05$).

Results and Discussion

Pineapple fruit used for research in the form of fresh fruit, ripe and yellow, no rotten and free of pests and diseases, and determined by the Indonesian Institute of Sciences (LIPI) Purwodadi Botanical Garden, Pasuruan-East Java. The juice was heated in a water bath to yield a viscous extract and aerosil was added then dried in oven at 50 °C. Standardized of dry extract include: organoleptic, loss on drying and chemical identification as in Table 3.

Table 3. Standardization of dry extract of pineapple fruit juice (Anonymous, 1989).

No.	Analysis	Reference	Results	Remarks
1.	Organoleptic:			
	- Color	Yellow	Yellow	Conformed
	- Odor	Aromatic	Aromatic	Conformed
	- Taste	Sweet	Sweet	Conformed
2.	Loss on drying	Not more than 8%	6.7%	Conformed
3.	Identification			
	- + 5 drops of concentrated H_2SO_4	Brown	Brown	Conformed
	- + 5 drops of H_2SO_4 10 N	Brown	Brown	Conformed
	- + 5 drops NaOH P 5% w/v in ethanol	Yellow	Yellow	Conformed
	- + 5 drops of NH_4OH (25%) P	Pale brown	Pale brown	Conformed
	- + 5 drops of $FeCl_3$ P 5% w/v	Yellowish brown	Yellowish brown	Conformed

Tablet prepared by wet granulation method, with concentration of PVP K-30 as binders 3%. To determine whether the resulting granules can be compressed into tablets, granules should be dry enough so it will not stick in the mold and has such a good flow and compressibility. The results of testing the quality of the granules as in table 4.

Table 4. Evaluation of the quality of granules

No.	Examination	Requirements	Results	Remarks
1.	The water content	2-5%	4.13 ± 0.18	Conformed
2.	Flow time	<10 seconds	8.36 ±.0.02	Conformed
3.	Repose angle	20-40 °	35.24 ± 0.04	Conformed
4.	Kompersibilitas (%)	5-18%	8.82 ± 0.03	Conformed

The results showed that granules have met the quality standard of good granules, namely the moisture content of 2-5% (Bandelin & Shangraw, 1989; Voigt, 1995), the flow time of less than 10 seconds (Voigt, 1995), the repose angle of 20-40° (Marshall, 1996), compressibility of 5-18% (Fierse & Hagen, 1996).

Good quality of tablets should meet the quality requirements as desired, including weight and dose uniformities, lack of incompatibilities, attractive appearance, as well as possible and efficient large scale production (Bandelin & Shangraw, 1989). The result of the quality of pineapple extract core tablet as in table 5.

Table 5. Evaluation of the quality of tablet

No.	Examination	Requirements	Results	Remarks
1.	Weight uniformity	X ± 5%	299.35 ± 1.35	Conformed
2.	Hardness	4-8 kgf	11.29 ± 0.29	Conformed
3.	Friability	≤ 1.%	0.34 ± 0.08	Conformed
4.	Disintegration time	< 15 minutes	7.79 ± 0.02	Conformed

Based on data from table 5, core tablet containing pineapple fruit juice demonstrated good weight uniformity since none of the tablets showed weight deviations of more than 5% (Anonymous, 1979), tablet hardness greater than the standard 4-8 kgf (Parrot , 1971) required that the tablet is resistant to collisions that occur during the coating process and not easily eroded or broken, friability of less than 1% (Banker & Anderson, 1996) and the tablet disintegration time of no more than 15 minutes (Anonymous, 1979).

Core tablet coated with Eudragit L100 solution concentration of 4% to weight coating layer 3% (FA), 4% (FB) and 5% (FC) can be seen in Figure 1. Test results generated coated tablets can be seen in table 6.

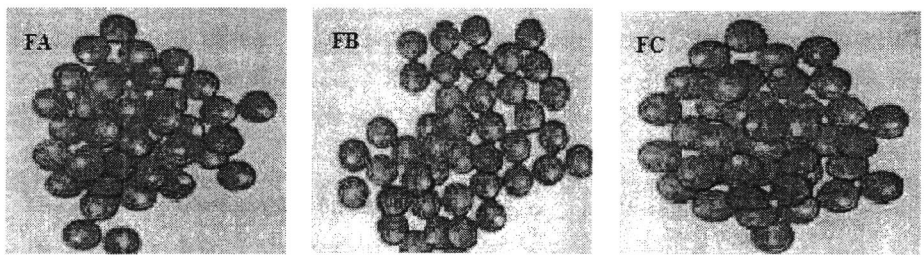

Figure1. Coated tablets of pineapple fruit extract: FA (3%), FB (4%) and FC (5%)

Table 6. Evaluation of coated tablet

No.	Examination	FA (3%)	FB (4%)	FC (5%)
1.	Weight of coating layer	3.31 ± 0.29	4.34 ± 0.33	5.43 ± 0.34
2.	Tablet hardness	14.41 ± 0.03	15.29 ± 0.13	16.06 ± 0.21
3.	Disintegration time	14.98 ± 0.26	17.61 ± 0.45	22.52 ± 0.81
4.	Visual inspection:			
	- +	6	3	3
	- ++	14	11	7
	- +++	84	83	90

Notes:
\+ : Rough tablet surface
++ : Rather rough surface
+++ : Smooth tablet surface

Statistical analysis by one-way ANOVA followed Tukey test ($p<0.05$) on the uniformity of coating layer weight for FA, FB and FC showed a significant difference. The greater weight of coating layer causes hardness and disintegration time increased probably due to the coating layer thickness so that the tablet strength increased and water is more difficult to get into the tablet.

Visual inspection by 10 panelists to 100 coated tablets produces smooth tablet surface as much as 83 : 83and 90 tablets, for FA, FB and FC respectively. Statistical analysis using Chi-Square ($p< 0.05$) showed there was no significant difference for surface smoothness FA, FB and FC coated tablet. Probably this caused by coating effect of 3 % weight coating layer in 300 mg tablet already produced smooth coating layer,so increasing the prosentage of coating layer to 4 and 5 % does not affect significantly the level of smoothness resulting coating layer.

The chromatogram profiles of tablet during manufacturing process: crude material, viscous extracts, granules and coated tablets using a-GF_{254} silica plate as a stationary phase and mixture of n-butanol: acetic acid: water (4:1:5, v/v) as a mobile phase, was observed in UV 254 and 366 nm corresponding to the content of flavonoids can be seen in figure 2. The results showed during the manufacturing process from the coated tablets, there is no difference of the spot and Rf value between the crude extract, viscous extract, granules and tablets.

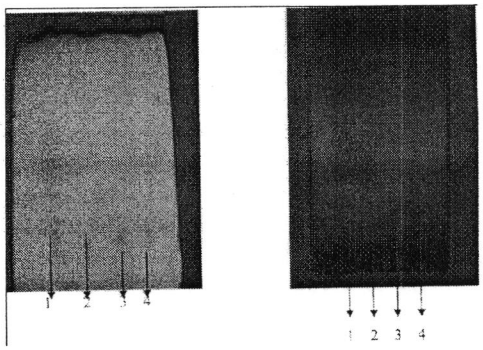

Figure 2. Chromatogram of constitutents in pineapple fruit juice, from crude materials ,viscous extract granules and coated tablets observed under UV 254 & 366. Notes: 1. Crude materials; 2. Viscous extract: 3. Granules; 4. Tablet.

Conclusions

Pineapple fruit extract can be formulated into enteric coated tablet dosage form using Eudragit L-100 as coating agent with weight of coating layer was 4%. During the manufacturing process of enteric coated tablet of pineapple fruit juice using wet granulation method, no changes in chemical compounds were observed.

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