

FAST-DISINTEGRATING TABLET FORMULATION OF GINGER (*ZINGIBER OFFICINALE* ROSC.) EXTRACT USING COPROCESSED EXCIPIENT OF PRE-GELATINIZED CASSAVA STARCH-ACACIA GUM

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ABSTRACT

Objective: Fast-disintegrating tablets (FDTs) are tablets that disintegrate and/or dissolve rapidly in the mouth, thereby helping patients who have difficulty in swallowing tablets. Ginger extract contains gingerol and is generally known for its antiemetic property. This study aimed to obtain and use coprocessed excipients of pre-gelatinized cassava starch (PCS) with acacia gum (AG) in FDT formulations of ginger extract.

Materials and Methods: In this research, five types of PCS-AG coprocessed excipients (Co-PCS-AG) were prepared by mixed PCS and AG with the following ratios mass of PCS and AG were 5:5, 6:4, 7:3, 8:2, and 9:1. The prepared Co-PCS-AG excipients were characterized in terms of morphology, particle size distribution, moisture content, pH, flow-ability properties, and swelling index. Based on the results, three types of Co-PCS-AG excipients, which were 7:3, 8:2, and 9:1, were selected for use in FDT formulation of ginger extract. The FDTs were then examined for tablet hardness, tablet friability, wetting time, and disintegration time.

Results: The results indicated that Co-PCS-AG 9:1 was ideal excipient to be used in FDT formulation, as it revealed good flow properties and swelling index compare to the other ratios. The Co-PCS-AG excipients were formulated into tablets and evaluated. Analysis of the ginger extract FDTs revealed that the FDT prepared using Co-PCS-AG 9:1 excipient had the best performance with tablet hardness, friability, wetting time, and disintegration time of 0.7 kp, 2.12%, 93 seconds, and 134 seconds, respectively.

Conclusions: Co-PCS-AG 9:1 excipient is a potential excipient with ideal binder, disintegrant, and filler properties for use in FDT formulation.

Keywords: Excipient, Acacia gum, Pre-gelatinized cassava starch, Fast-disintegrating tablet, Ginger extract.

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INTRODUCTION

Previous studies have investigated the use of cassava starch as a binder, filler, and disintegrant and its applications in tablets [1,2]. Several modifications exist that can help improve the properties of cassava starch, such as gelatinization. Furthermore, modified starches can also be combined with another excipient by coprocessing to obtain new excipient with good properties such as good flow-ability and compressibility.

Pre-gelatinized starch has been proven to have better flowability and swelling ratio compared to conventional starch [3]. Pre-gelatinized starch is formed by heating starch at its gelatinization temperature until the entire sample is gelatinized [2]. This pre-gelatinized starch has been proven to have a greater ability to expand than normal starch [4]. Pre-gelatinized starch can be combined with acacia gum (AG) using coprocessing to obtain an excipient that has the properties of a binder, filler, and disintegrant. AG has characteristics such as high solubility, low viscosity, and emulsification ability in water and oil [5].

In this study, cassava starch was physically modified by gelatinization to form pre-gelatinized cassava starch (PCS), then PCS was coprocessing with AG. It resulted in CS-AG coprocessed excipients (Co-PCS-AG), which was used in formulation of fast disintegrating tablets (FDT). In addition, ginger extract containing gingerol was used as a drug model in this study, as it has antiemetic property [5].

MATERIALS AND METHODS

Materials

Ginger extract (Xi'an Le Sen Bio-technology Co., Ltd., China), cassava starch (Sungai Budi Group), AG, mannitol (Roquette, France), aspartame

(Ajinomoto Co., Japan), gingerol standard (Chengdu Biopurify Phytochemicals Ltd., China), double-distilled water (PT. Ikapharmindo Putramas, Indonesia), acetonitrile (high-performance liquid chromatograph [HPLC] grade, Merck, Germany), and methanol (HPLC grade, Merck, Germany).

Methods

Synthesis of Co-PCS-AG excipients

In this study, Co-PCS-AG was prepared using a two-step process: First, cassava starch was gelatinized and second, it was coprocessed with AG. Cassava starch solution was heated to above 90°C. Simultaneously, AG was dissolved in water. PCS and AG were then mixed together by homogenizer with 3000 rpm for 30 minutes. The mixed PCS-AG was then dried with a drum dryer at ±80°C and sieved [6].

Characterization of Co-PCS-GA

Physical appearance

The physical features of Co-PCS-AG powder, including the shape, color, smell, and taste were evaluated.

Morphology

Morphology was observed under a scanning electron microscope (SEM).

Particle size distribution

Particle size distribution was observed by sieving Co-PCS-GA excipients. Briefly, five sieves with different pore sizes were arranged in descending order of size: 120, 80, 60, 45, and 35 µm, and vibrated at 30 rpm for 30 minutes.

Moisture content

Moisture content was observed with a moisture analyzer. A sample was placed on a calibrated moisture balance (Adam Equipment, Singapore), and the temperature in the chamber was increased up to 105°C. Co-PCS-GA excipients were weighed after they reached a constant weight at 105°C.

Acidity

Acidity measured by dissolving Co-PCS-GA excipients in distilled water at a concentration of 10% and the pH was measured using a pH-meter.

Compressibility index and flowability

The compressibility index of Co-PCS-GA excipients powder was measured using a bulk density tester (Erweka, Germany), and its flowability was measured with flowmeter (type GDT, Erweka, Germany).

Swelling index

Swelling index was determined by comparing the dry weight of Co-PCS-GA tablets and the weight after the Co-PCS-GA tablets were placed in 10 mL of water at different times.

Formulation and evaluation of ginger extract FDTs

Tablets were prepared by direct compression, which was mixing all ingredients until the homogeneous mixture was obtained (Table 1). The flowability of the mixed tablet mass was characterized including flow rate, angle of repose, compressibility index, and Hausner ratio. After that the mixed tablet mass was compressed into 200-mg tablet molds.

Evaluation of ginger extract FDTs

Organoleptic evaluation included appearance (color and shape) and the presence of physical defects. Size uniformity was evaluated on 20 tablets by measuring diameter and thickness of the tablets. Weight uniformity was evaluated by weighing 20 tablets on an analytical balance. Tablet hardness was measured using a hardness tester, while the friability was evaluated using a friabilator at 25 rpm for 4 minutes. The disintegrating time was evaluated by placing a tablet in a 10-cm-diameter dish and filling it with 10 mL of distilled water (37°C±0.5°C) [7]. The ginger extract FDTs were evaluated with a HPLC equipped with a reverse-phase C18 (Hypersil ODS column, 250 mm × 4.0 mm; internal diameter, 5 µm) with an isocratic elution system using a mixture of HPLC grade acetonitrile and water (55:45 v/v); flow rate of 0.6 mL/min, and a variable wavelength detector set at 282 [8].

RESULTS AND DISCUSSION

Synthesis of Co-PCS-AG

In this study, Co-PCS-AG excipients were prepared using a two-step process: First, cassava starch was gelatinized to forming PCS; and second, it was coprocessing with AG. Cassava starch solution was heated to above 90°C. Simultaneously, AG was dissolved in water. PCS and AG dispersions were then mixed by homogenizer at 3000 rpm for 30 minutes, then dried with a drum dryer, and sieved through a 60-mesh sieve. Five types of Co-PCS-AG excipients were produced with the following mass ratios of PCS and AG: 5:5, 6:4, 7:3, 8:2, and 9:1. The Co-PCS-AG yield is shown in Table 2.

Characterization of Co-PCS-AG excipients

Physical appearance

Co-PCS-GA excipients were a fine, odorless, and brownish-white powder. AG contributed to the brown of the PCS-AG powder, while cassava starch by itself is white.

Morphology

Co-PCS-AG excipients were morphologically analyzed under an SEM. As seen in Fig. 1, the Co-PCS-AG excipients powders have irregular-shaped flakes. This shape of the powder was due to the drying process using a double drum dryer, which breaks the starch granules into thin, irregular flakes. The ideal shape to obtain good flow properties is spherical [9].

Particle size distribution

Particle size distribution was studied using the sieve method. Five sieves with different pore sizes were arranged in descending order of mesh size: 120, 80, 60, 45, and 35 µm. Then, 20 g of Co-PCS-AG was placed on the sieve, which was vibrated for 3000 rpm for 30 minutes. Each sieve was then weighed to calculate the mass of Co-PCS-AG on the sieve. Fig. 2 shows the particle size distribution of Co-PCS-AG. In Fig. 2, it can be seen that the particle size of Co-PCS-AG was distributed in various sizes, with most of the particles <125 µm. The results showed that more than 77% of Co-PCS-AG 5:5 excipient had a powder size of <125 µm, whereas only 33.5% of Co-PCS-AG 9:1. Particle size variation of Co-PCS-AG excipients was influenced by strength and length of the powder milled. The particle size can affect the flowability of the excipient powder. The smaller the particle size, the slower will the flow rate be [10]. Excipient powder of >250 µm particle size usually have a good flow rate. Particle size of <100 µm will have the high cohesion and exhibit problems with the flow rate [11].

Moisture content

Measurements of moisture content showed that Co-PCS-AG 5:5 had higher water content than other coprocessed excipients (Table 3). Co-PCS-AG 8:2 showed the lowest moisture content. The difference in the moisture content may be related to the differences in the percentage of AG used in the coprocessing step. AG has a high hygroscopicity. The higher the AG content, the higher will the moisture content of the excipient be, while lower percentage of AG used in the coprocessing will translate to excipient with a reduced moisture content. Excipient with very high-water content will result in poor flowability. High-moisture content increases the adhesion force between the particles [12].

Acidity

pH was measured using a 10% solution of Co-PCS-AG in distilled water. The result revealed that there were no significant differences in pH between the different compositions of Co-PCS-AG excipients. The pH of all the excipients was in the range of 5.11-5.41 while the pH of PCS was 6.69. A decrease in the pH of Co-PCS-AG excipients may be because AG is more acidic than PCS, as the pH of AG is 4.5-5 [13].

Table 1: Formulation of ginger extract FDTs

Ingredients (mg)	Formulation 1 Co-PCS-AG excipient (7:3)	Formulation 2 Co-PCS-AG excipient (8:2)	Formulation 3 Co-PCS-AG excipient (9:1)	Formulation 4 Co-PCS-AG excipient (9:1) without avicel	Formulation 5 PCS-AG excipient (9:1) physical mixing
Ginger extract (mg)	100	100	100	100	100
Co-PCS-AG (mg)	50	50	50	75	50
Mannitol (mg)	20	20	20	20	20
Aspartame (mg)	5	5	5	5	5
Avicel pH-102	25	25	25	-	25
Total (mg)	200	200	200	200	200

Co-PCS-AG: Coprocessed-pre-gelatinized cassava starch-acacia gum, FDT: Fast-disintegrating tablets

Flowability

Table 4 presents the results of flowability properties of the FDTs mass, which is represented with flow rate, angle of repose, compressibility index, and Hausner ratio. In general, Co-PCS-AG 9:1 excipient had better flowability properties than other excipients.

Table 2: Yield value of Co-PCS-AG excipients

PCS-GA mixture	Dried Co-PCS-AG excipients (%)
5:5	48.22
6:4	43.37
7:3	47.24
8:2	54.65
9:1	67.16

Co-PCS-AG: Coprocessed-pre-gelatinized cassava starch-acacia gum

Table 3: Moisture content and acidity

Excipient	Moisture content (%)	pH
Co-PCS-AG 5:5	6.02±0.36	5.17±0.04
Co-PCS-AG 6:4	4.64±0.31	5.15±0.04
Co-PCS-AG 7:3	4.55±0.54	5.11±0.12
Co-PCS-AG 8:2	3.72±0.15	5.31±0.08
Co-PCS-AG 9:1	3.78±0.23	5.41±0.22

Co-PCS-AG: Coprocessed-pre-gelatinized cassava starch-acacia gum

Swelling index

The swelling index of excipient in a medium will affect the disintegration time of the tablets [14]. Swelling indices were calculated by measuring the increase in weight of Co-PCS-AG tablet at various time points. Fig. 3 shows that in the first 5 minutes, Co-PCS-AG tablets swelled rapidly in water. After 2 hrs, there were no significant differences in the swelling index. Co-PCS-AG 9:1 excipient had the largest swelling index compared to all excipients, suggesting that Co-PCS-AG 9:1 can be prospectively used in the formulation of FDTs as a disintegrant. The difference in the swelling index of different Co-PCS-AG excipients can be due to the different percentages of AG used in their preparation. AG has slower water absorption than PCS. The higher the percentage of AG used in the preparation, the lower was the swelling index observed.

Formulation and evaluation of FDTs of ginger extract

After the excipients were mixed with ginger extract, the FDTs mass were evaluated. Table 5 presents the flowability of FDTs mass. In general, all mass had poor flowability. This is because the influence of ginger extract percentage used in the FDTs formulation was too large. Furthermore, the particle size of ginger extract was too small. More than 85% of the ginger extract sample used had a particle size of <125 µm. The smaller the particle size of a powder, the worse the flow rate [15]. Particles sizes of >250 µm usually have a good flow rate. Particle size of <100 µm will result in high cohesion and poor flow rate [16].

Table 4: Flowability of Co-PCS-AG excipients

Excipient	Flow rate (g/detik)	Angle of repose	Compressibility index (%)	Hausner ratio
Co-PCS-AG 5:5	1.93±0.71	37.27±5.74	33.7±2.96	1.55±0.05
Co-PCS-AG 6:4	7.93±0.62	31.26±1.84	32.08±1.25	1.51±0.02
Co-PCS-AG 7:3	6.78±0.24	31.49±0.09	33.10±3.42	1.49±1.56
Co-PCS-AG 8:2	8.70±0.91	31.32±1.50	30.87±1.13	1.38±1.41
Co-PCS-AG 9:1	9.55±0.11	31.36±1.29	30.83±0.57	1.44±1.45

Co-PCS-AG: Coprocessed-pre-gelatinized cassava starch-acacia gum

Table 5: Flowability of FDT formulation

Formulation	Flowability (g/s)	Angle of repose (°)	Compressibility index (%)	Hausner ratio
F1	0.96	51.42±6.68	21.10±0.00	1.26±0.00
F2	1.18	52.2±1.00	21.73±0.02	1.27±0.04
F3	1.14	49.7±2.74	21.47±0.02	1.27±0.04
F4	1.02	49.51±2.74	21.39±0.04	1.27±0.08
F5	0.95	53.32±1.70	21.54±0.02	1.27±0.04

FDT: Fast-disintegrating tablets

Table 6: Physical characteristics of FDTs of ginger extract

Formulation	Average weight (mg)	Diameter (mm)	Thickness (mm)	Ginger extract content (%)
F1	201.48±0.87	8.16±0.03	3.6±0.05	87.43±1.55
F2	201.20±1.40	8.13±0.02	3.6±0.06	89.65±2.63
F3	201.20±0.67	8.13±0.01	3.5±0.08	86.97±1.21
F4	204.60±0.87	8.11±0.01	3.8±0.03	89.00±2.40
F5	203.84±1.49	8.11±0.01	3.6±0.03	89.02±1.51

FDT: Fast-disintegrating tablets

Table 7: Evaluation of FDTs of ginger extract

Formulation	Hardness (kPa)	Friability (%)	Disintegration time (s)	Wetting time (s)
F1	0.70±0.01	1.82	283±43	288.33±17.61
F2	0.70±0.02	2.03	257±16	186.66±83.18
F3	0.70±0.02	2.12	134±6	93.66±6.50
F4	0.69±0.02	6.20	260±16	83.33±11.23
F5	0.71±0.01	4.16	154±18	113.66±4.72

FDT: Fast-disintegrating tablets

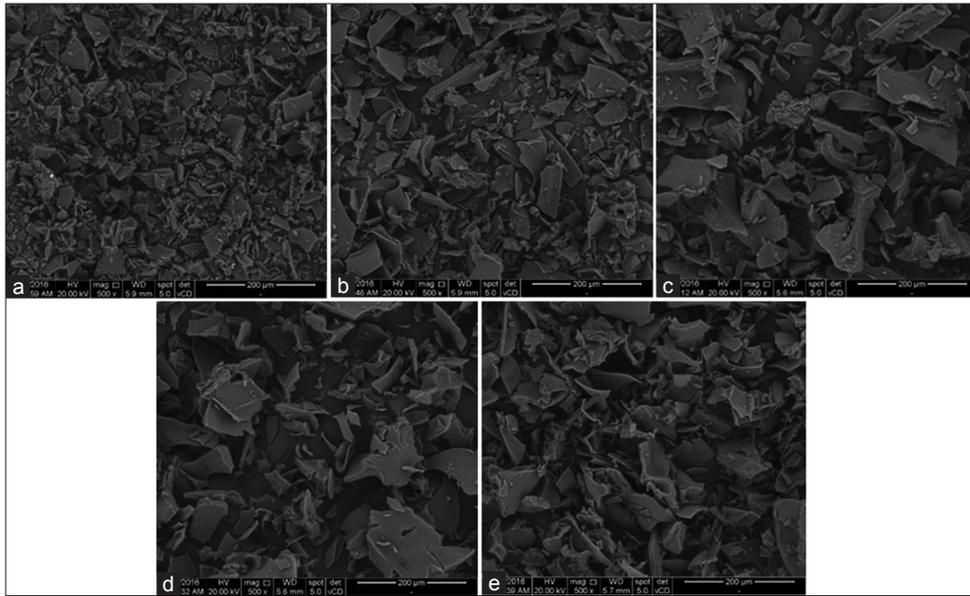


Fig. 1: Scanning electron microscope micrographs of coprocessed-pre-gelatinized cassava starch-acacia gum (Co-PCS-AG) with magnification of $\times 500$. (a) Co-PCS-AG 5:5, (b) Co-PCS-AG 6:4, (c) Co-PCS-AG 7:3, (d) Co-PCS-AG 8:2, (e) Co-PCS-AG 9:1

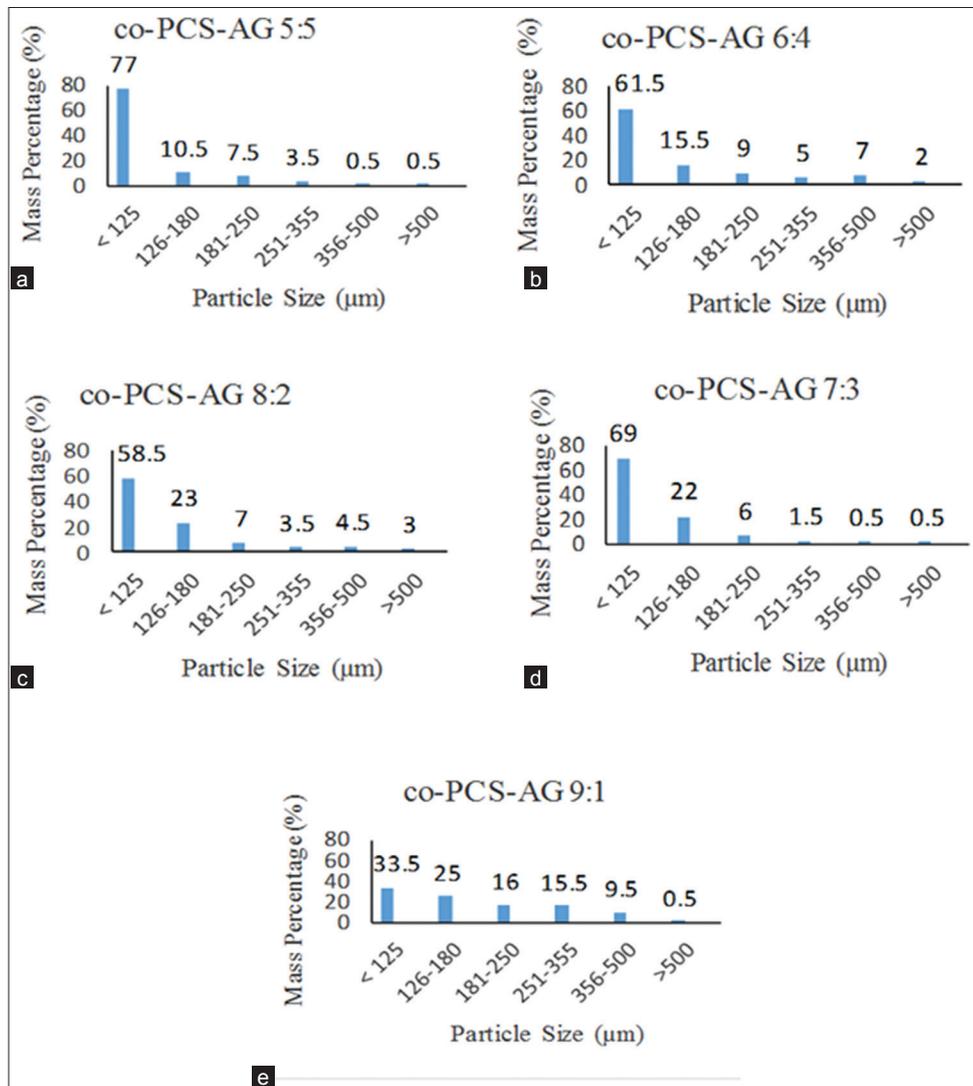


Fig. 2: Particle size distribution of coprocessed-pre-gelatinized cassava starch-acacia gum (Co-PCS-AG) excipients. (a) Co-PCS-AG 5:5, (b) Co-PCS-AG 6:4, (c) Co-PCS-AG 8:2, (d) Co-PCS-AG 7:3, (e) Co-PCS-AG 9:1

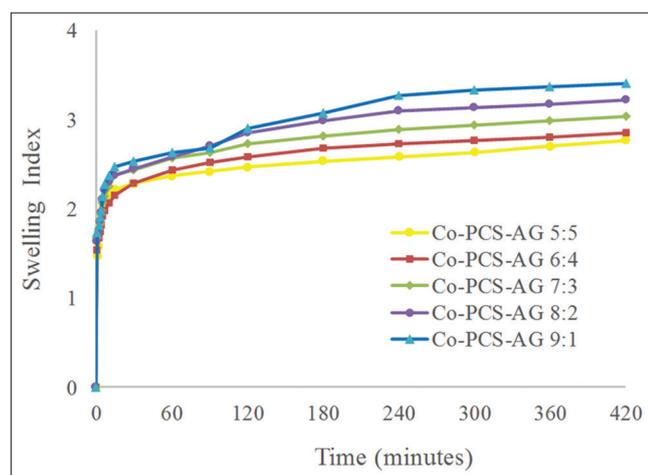


Fig. 3: Swelling index of coprocessed-pre-gelatinized cassava starch-acacia gum excipients

Evaluation of ginger extract FDTs

Table 6 shows the evaluation results of the ginger extract FDT. As seen in the table, the average of size and weight of the ginger extract FDTs completely follow the requirements of the tablet standard. In addition, the ginger extracts content in FDTs in the range of 86.97 – 89.02%. All types of ginger extract, FDTs indicated a decreasing in content of ginger extract, which was marked with its gingerol content. This might be caused there were oxidation of gingerol during FDTs preparation.

The important evaluations for FDTs are tablet hardness, friability, wetting time, and disintegration time, which is represented at Table 7. The lower hardness of this tablet will affect its friability. The result of the friability test showed that all the formula did not comply with the requirement of the conventional tablets. The high friability can be addressed using individual blister packaging [17,18]. The F4 FDTs showed the fastest wetting time, although it was not containing Avicel. Meanwhile, the fastest disintegration time was observed in F3 FDTs. It is because F3 FDTs used PCS-AG 9:1, which had the best swelling index and the biggest particle size among all Co-PCS-AG excipients.

CONCLUSION

Five types of Co-PCS-AG excipients have been produced and studied for their characteristics, and the results indicated that Co-PCS-AG 9:1 was ideal excipient to be used in FDT formulation. Evaluation of the ginger extract FDTs revealed that the FDT prepared using Co-PCS-AG 9:1 excipient had the best performance with tablet hardness, friability, wetting time, and disintegration time of 0.7 kp, 2.12%, 93 seconds, and 134 seconds, respectively. It could be concluded that Co-PCS-AG

9:1 excipient is a potential excipient, which represent an ideal filler, disintegrant, and binder properties for use in FDTs formulation.

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