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The effect of partially pregelatinized cassava starch as disintegrant for paracetamol tablet

Okta Nama Putra[1*], Winni Nur Auli[2], Musa[1], Derina Paramitasari[1], Gabriela Kasih Mawarni[1]

[1]Research center for Agroindustry- National Research and Innovation Agency (BRIN)
Jl. Raya Puspiptek, Kota Tangerang Selatan, Banten, Indonesia
[2]Department of Pharmacy at Sumatera Institute of Technology
Jl. Terusan Ryacudu, Way Huwi, Jati Agung, Lampung Selatan, Indonesia

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ABSTRACT

The use of partially pregelatinized starch in tablet formulations is entirely various; one of them is disintegrant. Present pregelatinized starch is imported from another country, which is relatively expensive. In contrast, many plants can be used as starch sources, including cassava which is relatively abundant in Indonesia. This study aimed to determine the effect of using partially pregelatinized starch from cassava as a disintegrant in paracetamol tablets. In this study, seven formulas were used with different disintegrants, three formulas using partially pregelatinized starch from cassava with concentrations of F1 5%, F2 10%, and F3 15%, three formulas using Starch 1500 with the same concentration as partially pregelatinized starch from cassava and one control formula without disintegrant. The tablet was made using the wet granulation method. The tablets produced were tested for physical properties (hardness, disintegration, and dissolution). In addition, compact ability of partially pregelatinized starch from cassava was compared with Avicel, Starch 1500, and cassava starch. Based on the results of the study showed that partially pregelatinized starch from cassava produced tablets that tended to be capping with less hardness than tablets with Starch 1500 and control tablets. The compact ability test results showed that the compact ability of partially pregelatinized starch from cassava was better than Starch 1500 and cassava starch. The disintegration test results showed that tablets with partially pregelatinized starch from cassava had faster disintegration than tablets with Starch 1500 and control tablets. The dissolution profile of tablets with partially pregelatinized starch from cassava is also better than other formulas.

Keywords: partially pregelatinized cassava starch, disintegrant, paracetamol, tablet

Corresponding author:
Okta Nama Putra
Research center for Agroindustry- National Research and Innovation Agency (BRIN)
Gedung Technology Management Center (TMC)
Jl. Raya Puspiptek, Kota Tangerang Selatan, Banten
Email: okta005@brin.go.id

INTRODUCTION

Excipient is the core of drug delivery systems, especially in pharmaceutical solid dosage form (Van Der Merwe et al, 2020). Starch has carbohydrate polymer structures that can be utilized in various materials for the food, chemical, and pharmaceutical industries. In pharmaceutical industries, starch and its derivatives are used as different types of excipients in tablets, such as disintegrants, fillers, lubricants, and a binding agent (mucilage) (Zhang et al., 2013). Industrial interest is to develop modified starch from native starch to get better properties of release profile solid dosage form, especially from starch as a binder or disintegrant (Garba Mohammed, 2017).

Pregelatinized starch is one modification which chemically and or mechanically processed to partially or entirely destroy the starch granules (Rahayuningsih et al., 2010). Pregelatinized starch can be used in tablets to improve flowability, disintegration, and hardness (Rowe et al., 2009). Some research about pregelatinized starch from various kinds of starch has been reported to have suitable characteristics as a binder and disintegrant for tablets (Ningsi et al, 2016; Sui et al, 2018). Fully pregelatinized starches are being used as binders in solid dosage form formulations. However, due to gelatinization, many disintegration properties are lost (Rahman et al., 2008).

On the other hand, partially pregelatinized starches (PPS) have a mixture of properties of both native and fully gelatinized starches (Adedokun & Itiola, 2010). PPS is one of the starch derivatives that can be used as a potential disintegrant agent in oral solid dosage formulation, in which it can be produced by modifying some or all starch granules with chemical, physical and/or mechanical processing, such as esterification, etherification, drum drying, extrusion, spray drying and stirring ball (Lawal, 2019). Generally, PPS consists of 5% free amylose, 15% amylopectin, and 80% native starch (Rowe et al., 2009). Some of the advantages of PPS are that its granules have better flow properties, are easier to dilute in water, have higher swelling rather than its native, and can be compressed directly. In contrast, fully pregelatinized starch is easily diluted in cold water, which can be applied as a binder agent in wet granulation (Choiri et al., 2018). Moreover, the higher swelling of starch gives better quality disintegrant agents for tablets (Sulaiman et al., 2020). Disintegrant has a critical role in resisting pressure, especially in the release process of tablet preparations.

Cassava starch is a common natural starch used. According to Statistics Indonesia, cassava has become one of the primary commodities in Indonesia, with its annual domestic production amounts were more than 24 million tonnes in 2015, and it increased to 27 million tonnes in 2016. Therefore, Indonesia is the third largest cassava producer after Nigeria and Thailand, so its massive production can be the potential to produce pharmaceutical-grade native starch as an excipient in formulating tablets. Cassava starch amylose content was 18.0%, and the amylopectin content was 60.15 (Nisah, 2018). Both fully and partially pregelatinized grades are commercially available. One of the most commercial pharmaceutical grades of partially pregelatinized starch is Starch 1500, which is imported and expensive (Svačinová et al., 2021). However, locally produced pregelatinized starch has not been fully developed and applied in formulating pharmaceutical tablets.

Paracetamol is the principal para-aminophenol derivative in use. Paracetamol has analgesic and antipyretic properties and weak anti-inflammatory activity. The mechanism of analgesic action remains fully elucidated but may be due to the inhibition of prostaglandin synthesis both centrally and peripherally. Paracetamol is used to relieve mild to moderate pain and minor febrile conditions. Paracetamol and NSAIDs are the first choice analgesics for treating mild to moderate pain and are also used in moderate to severe pain to potentiate the effects of opioids. For pain management, paracetamol is recommended as the drug of the first choice (Sweetman, 2009). Paracetamol is orally administered as a tablet preparation (Krishnat et al., 2017).

Wet granulation is commonly used in manufacturing tablets because it improves uniformity and compressibility (Chen et al., 2022). In this paper, the cassava-based partially pregelatinized starch is used in paracetamol tablets, and the tablet characteristics are compared with paracetamol tablet formulation using Starch 1500.

MATERIALS AND METHOD

Materials

The main equipment in this research are a mixed steamer, feeder, screw extruder, mill dryer, weight scale analytical balance, cube mixer (Erweka, Germany), laboratory sieve 14 mesh, 16 mesh, 80 mesh (Endecotts, England), Fluid Bed Dryer (Edencotts, England), single punch tablet (Korsch), thickness gauge (Mitutoyo), stopwatch, disintegration tester (Erweka, Germany), dissolution tester (Erweka, Germany), spectrophotometer UV-Vis, whiteness tester, pycnometer, hardness tester (Monsanto), flowability tester (Erweka, Germany), polarization microscope (Primotech, Zeiss, Germany), moisture content analyzer, pH-meter, viscometer, centrifuge, Standard Test Sieve no. 60, 80, 100, and 140, and tap density tester (Erweka, Germany).

Materials that are used in this research are paracetamol (Anqiu Lu'an Pharmaceutical, China), native cassava starch, Starch 1500 (Colorcon, USA), magnesium stearate, fumed silica, Avicel, lactose (PT. DMS, Indonesia), and aqua dest.

Methods

Partially pregelatinized starch production

Native cassava starch with a moisture content of 30% was cooked with mix steamer at 70ºC for 15 minutes then the cooked starch dough was extruded with a screw extruder through a feeder (3.5 Hz). The screw extruder frequency is 12.5 Hz with barrel temperatures 1 and 2 off and barrels temperature three at 50ºC. The flakes from the extruder were dried using a mill dryer at 120 – 200ºC to produce a dried starch powder. Then, the powder was sieved with a standard test sieve of 80 mesh.

Characterization of partially pregelatinized starch

Organoleptic test

One gram of partially pregelatinized starch was observed in the shape of the particle, color, odor, and taste (Indonesian Ministry of Health, 1995). The whiteness degree of partially pregelatinized starch was measured with a whiteness tester.

Morphology test

The 100 mg of partially pregelatinized starch was added with two drops of water in object glass, and observed the hilus and lamella of starch were under a polarization microscope.

Moisture content

The 500 mg of partially pregelatinized starch was analyzed its moisture content with a moisture *content analyzer.*

pH measurement

Partially pregelatinized starch was mixed with aqua dest to make 10% wt. of suspension, and the suspension was measured its pH at 25ºC with a pH meter.

Viscosity

Partially pregelatinized starch was added with water to form 10%wt suspension, and its viscosity was measured with a viscometer at 25ºC.

Cold water solubility

Two (2) grams of partially pregelatinized starch were mixed with 100 mL of water and stirred for 20 minutes. Then, the starch suspension was centrifuged at 2500 rpm for 30 minutes. The 25 mL of supernatant was placed on a petri dish, where the constant weight was measured (W_0); then, it was heated in a water bath until nearly dry and put in the oven at a temperature of 105ºC for 3 hours. After that, the petri dish was dehumidified and cooled down in a desiccator for 15 minutes until the weight

was constant. Subsequently, the dried sample on the petri dish was weighed (W). The coldwater solubility can be calculated with Equation 1 (Jivan et al., 2014).

$$Sc\ (\%) = \frac{(W - W_o)\ x\ 4}{Sample\ Weight\ (g) x\ (100\% - \%Moisture\ Content)}\ x\ 100\% \quad (1)$$

Flow time and angle of repose

One hundred (100) grams of partially pregelatinized starch was weighed and put in the funnel of Flow Time and Angle equipment. Then, the funnel bottom was closed, and let the equipment measured the flow time and angle of repose of the sample.

Bulk density and tapped density

One hundred (100) grams of partially pregelatinized starch was weighed and put in a measuring cylinder of 200 ml (the volume was recorded as bulk volume). Then, the cylinder was tapped until the volume was constant (Tapped Volume, V). Tapped density was calculated as a ratio of 100 mg/tapped volume. Bulk density was calculated as a ratio of 100 mg/bulk volume.

Compressibility index and hausner ratio

The compressibility index and Hausner ratio were determined with Equations 2 and 3 using tapped density and bulk density have been calculated.

$$\text{Compressibility Index} = 100 \times [(\text{Tapped density} - \text{bulk density})/\text{tapped density}] \quad (2)$$

$$Hausner\ Ratio = \frac{Bulk\ Volume\ (ml)}{Tapped\ Volume\ (ml)} \quad (3)$$

Compaction ability

Two hundred (200) mg of starch sample were weighed and put in suitable dye diameter, followed by compressing the sample with a specific punch diameter. The compressed tablets was measured in its diameter, thickness, and hardness. The data results were converted with a calibration equation (Choiri et al., 2018).

Preparation of paracetamol tablet by wet granulation

Tablet was prepared by the wet granulation method. Paracetamol was mixed well with lactose; then, it was moistened with mucilage amylum 10% to wet masses. The dough was sieved with mesh no.14 until granules were formed. Then, the granules were dried using Fluid Bed Dryer for 40 minutes until the moisture content was under 1%. The dried granules were sieved again with mesh no.16 to become dried powder with uniform size. Further, the dried powder was mixed well with partially pregelatinized cassava starch and Starch 1500 with different compositions. It was followed by adding magnesium stearate and fumed silica to make a homogenous mixture. After that, the mixture was compressed using a compressed tablet machine with a die diameter of 13 mm to produce a 700 mg tablet. The various compositions of the mixtures are shown in Table 1.

Evaluation of tablets

All tablets were evaluated for their organoleptic, hardness, and disintegration time. For tablet organoleptic, tablets were observed for size, shape surface, color, and any physical defects. Tablet hardness, tablets were placed well in a hardness tester and then rotated down to give pressure to the tablet until the tablet was broken. The hardness was observed in kilograms. Disintegration time was

tested for ten tablets samples were placed inside a cylinder tube dan a disk was put in each tube. Warm water at the temperature of 37º ± 2ºC was used as media. Next, the disintegration tester was switched on until all the tablets inside the tube were disintegrated or there was no transparent tablet core, and the disintegration time was measured.

Table 1. Paracetamol tablet formulations with various concentrations ingredients

Composition	Function	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)
Paracetamol	API	500	500	500	500	500	500	500
Lactose	Filler	148	113	78	148	113	78	183
Musilago amylum 10%	Binder	10	10	10	10	10	10	10
Partially Pregelatinized Cassava Starch	Disintegrant	35	70	105	0	0	0	0
Starch 1500	Disintegrant	0	0	0	35	70	105	0
Magnesium Stearate	Lubricant	5.6	5.6	5.6	5.6	5.6	5.6	5.6
Fumed silica	Glidant	1.4	1.4	1.4	1.4	1.4	1.4	1.4
	Total Weight	700	700	700	700	700	700	700

Note:

F1: Tablet with 5% of partially pregelatinized starch as disintegrant
F2: Tablet with 10% of partially pregelatinized starch as disintegrant
F3: Tablet with 15% of partially pregelatinized starch as disintegrant
F4: Tablet with 5% of Starch 1500 as disintegrant
F5: Tablet with 10% of Starch 1500 as disintegrant
F6: Tablet with 15% of Starch 1500 as disintegrant
F7: Tablet without disintegrant

Dissolution study

The test was done using dissolution tester type 2, a paddle with 50 rpm. The dissolution media was 900 ml of a phosphate buffer solution with pH 5.8, and the temperature was 37°C ± 1°C. Several sampling points were chosen at 5, 10, 15, 20, 30, and 45 minutes. Paracetamol concentration was determined using Uv-Vis Spectrophotometer with a wavelength of 243 nm (Ditjen POM, 2020).

RESULT AND DISCUSSION

PPS modification from native cassava starch leads to the production of superior properties of natural cassava starch. Partially pregelatinized cassava will have improved functionality, including flowability, compressibility, and cold-water solubility. PPS modification leads to a distinctive concentration of amylose and amylopectin. Amylose contains a straight-chain molecular structure, showing solid intermolecular bonding capability. Amylose swells altogether when wetted, giving it fabulous disintegrating characteristics. Amylopectin contains a branched-chain atomic structure, which makes it prepared dissolvable in cold water. Amylopectin capacities are filler granulation forms (Agama-Acevedo et al, 2018). PPS contains about 28% of amylopectin and 72% of amylose (Lefnaoui & Moulai-Mostefa, 2015).

Characterization of partially pregelatinized cassava starch (PPCS)

Characterization of PPCS related to swelling extent, compressibility, and flow of properties of modified starch. Partially pregelatinized cassava starch produced in this research has a fine white powder with a slightly distinctive cassava odor and is tasteless. Microscopically native starch has characteristics according to Indonesian Pharmacopeia (2014) in which the starch forms a slightly rounded, single grain and hilar visible in the middle (Putra et al., 2018). Native cassava starch granules are spherical with smooth surfaces (Zhang et al., 2013). Microscopic test of PPCS by polarization microscope observed starch granule shapes ruptured because the gelatinization process showed rough surfaces and irregular particles (Figure 1). In PPCS, most of the granule was ruptured after being observed under 40x magnification. However, few granules still have their natural characteristic, like native starch, indicating partially pregelatinized cassava starch has formed.

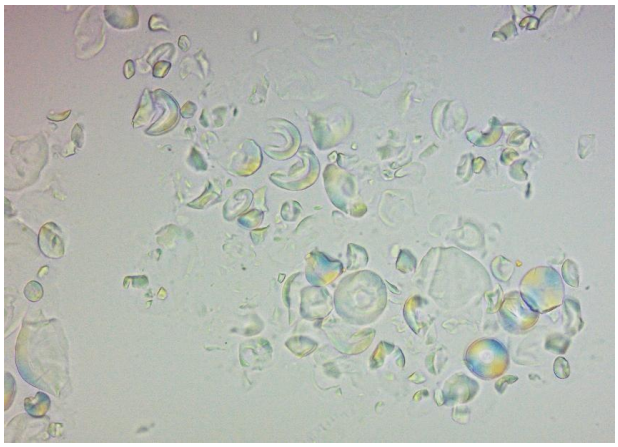

Figure 1. Partially pregelatinized cassava starch observation under polarization microscope with 40x Magnification

The ruptured starch of PPCS can increase amorphization and improve the rate of moisture entry, which is widely recognized as the primary step in the disintegration and deaggregation processes of tablets and granules (Riley et al., 2008). This result promotes PPCS' better disintegration properties and indirectly affects drug dissolution from solid dosage forms (Zhang et al., 2013).

Partially Pregelatinized Cassava Starch has high viscosity and cold-water solubility values (Table 2). The solubility of starch in cold water is an evaluation of the degree of gelatinization of starch, and the more excellent solubility indicates a higher degree of gelatinization. The ruptured structure of starch gives partial cold-water solubility. PPCS exhibits dual functionality in granulation applications as both binder and disintegrant due to partial cold-water solubility (Zhang et al., 2013). The flow characteristic of PPS gives a good result based on the flow rate that meets the requirements. Compressibility index values of PPCS indicated good flow character (Carr, 1965). The angle of repose PPCS indicates a fair result but is still manufactured satisfactorily (Carr, 1965; U.S. Pharmacopeia, 2018).

Mechanical strength is an essential parameter that represents inter-particulate bonding. For tablet dosage form, it is recommended to determine the dominant ingredient's mechanical properties to predict the tablet's overall compressional behavior (Amin et al., 2012). One of the mechanical strengths is the compaction ability test. This test was carried out to determine the bonds between the powders. A firm bond may prevent disintegration, subsequent dissolution, and solubility (Ogungbenle, 2009). An enormous compaction ability value (tensile strength indicated poor bonding between powder masses (Dewi et al., 2021). Compaction ability characteristic of PPCS showed a higher value in tensile strength with the same compression force than Starch 1500 and native cassava starch but lower than avicel. As shown in Figure 2, partially pregelatabletinized cassava starch has higher tensile strength than Starch

1500 and native cassava starch. This result indicated the disintegration ability of PPCS lower than Starch 1500 and native starch. Avicel is also a comparative disintegrant that acts as an excellent disintegrant and delays the dissolution rate impressively (Hoag, 2017).

Table 2. Preliminary test result cassava-based partially pregelatinized starch

Parameter	Unit	Results
Whiteness	%	83.6
Moisture Content	%	3.36
pH		5.64
Viscosity	cP	82
Cold water solubility	%	10.14
Flow Rate	g/second	16.26
Angle of Repose	degree	37.48
Tapped Density	g/mL	0.719
Bulk Density	g/mL	0.609
Compressibility Index	%	15.22
Hausner Ratio		0.848

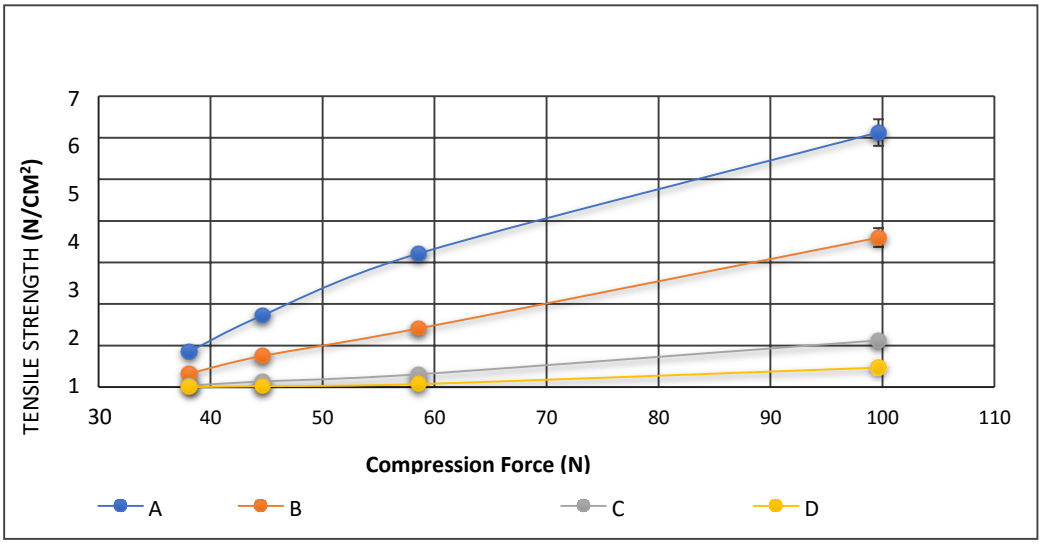

Figure 2. Compaction ability profile of A: avicel, B: partially pregelatinized cassava starch, C: Starch 1500, and D: native cassava starch

Evaluation of tablets

This research compared the effect of using PPCS and starch 1500 as disintegrants in the formulation of paracetamol tablets. Tablets were prepared with seven formulas with various disintegrant percentages and fillers. Formula F7 was formulated as a control that does not have disintegrated characteristics, so the evaluation can be done reasonably. The F7 Tablets have the required shape, and the hardness value is high, which is 8.65 kg (Table 3), and the result is the same with F4-F6 Tablets. On the contrary, the F1-F3 Tablets have dents, and the hardness values are less than 5 kg. The excellent

hardness is between 4 kg-8 kg (Lachman et al., 2008). Tablets with ingredients of PPCS starch have a lower hardness than tablets that use cassava starch. Therefore, the hardness results are contradicted by the compaction ability results.

Table 3. Physical test results of tablets

Parameter	Partially Pregelatinized Cassava Starch			Starch 1500			Control
	F1	F2	F3	F4	F5	F6	F7
	5%	10%	15%	5%	10%	15%	0%
Physical Appearances	The tablets are dent with low hardness			The tablets have a good shape and no dent			
Tablet Hardness (kg)	4.26±0.526	4.03±0.402	3.61±0.248	8.25±0.984	8.33±0.688	7.88±0.800	8.65±0.711
Disintegrated Time (minutes)	30.62±5.79	21.83±4.24	26.16±9.62	35.66±16.05	41.81±10.61	36.13±2.61	115.45±5.20

Some researchers stated that starch has elastic deformation ability during compression, so the tablet compression is not strong enough because of the weakness of intermolecular bonds. However, other researchers also found that the starch granules will be broken and become plastic deformation if compressed with more than 2000 kP (Choiri et al., 2018). This finding can be the main cause for partially pregelatinized starch granules being broken during the compression, so the results differed between compact ability and hardness. In addition, the different compact ability results between cassava-based partially pregelatinized starch, and other starch also can be affected by its characteristic that can not bond to other materials during tablet production.

The percentage of drug release shows a significant influence on the binding strength of the tablet (Putra et al., 2018). The disintegration characteristic of the tablet is mainly caused by the porosity of the tablet that is formed during the compression process. In detail, high compression provides lower porosity and minimizes the capillarity of the tablets to prevent water interventions (Choiri et al., 2018). Suppose the water readily intervenes the tablet's capillary structure with high porosity. In that case, the water will fulfill the void structure during the swelling process, and the starch granules will be broken out easily. This conforms with the disintegration time of a tablet made from PPCS faster than a tablet made from Starch 1500.

The fast disintegration time causes the dissolution of the active substance to be too fast so that the drug's therapeutic effect is also faster (Apriani & Arisanti, 2009). Moreover, the dissolution profile of the tablet with partially pregelatinized starch formulation was higher than the tablet with Starch 1500 formulation, as shown in Figure 3. The dissolution rate was related to the discharge percentage of paracetamol in the tablet. Furthermore, the higher concentration of partially pregelatinized starch in tablet formulations significantly results in a higher percentage of the tablet. Therefore, it shows that PPCS also has the potential to be the disintegrant that can substitute the imported one.

The F1-F3 tablets have dents on the edge, so it needs to be compressed several times, giving various tablet weights. Further, there is no need to conduct mass uniformity and friability test because the hardness values are low. The character of PPCS indicated a better dissolution profile (Azubuike et al, 2019).

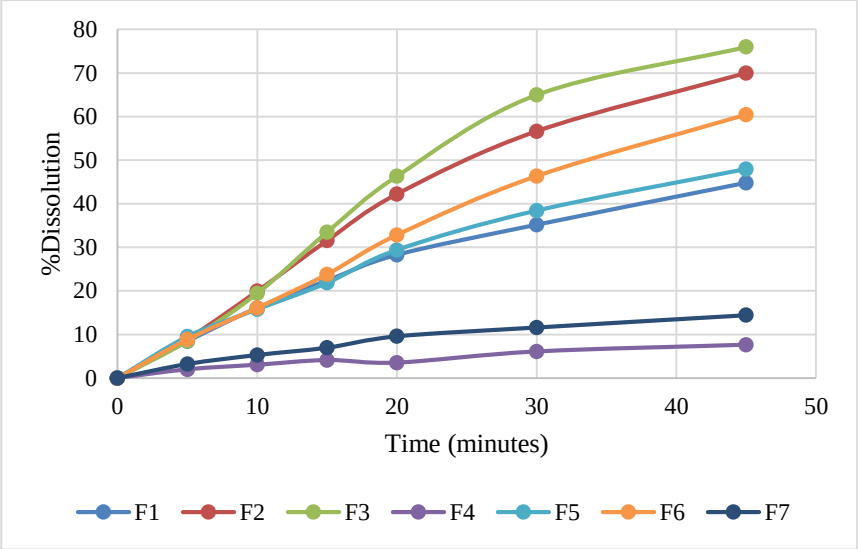

Figure 3. The dissolution profile of PPCS compared to starch 1500

CONCLUSION

Cassava-based partially pregelatinized starch profiles show the potential to be qualified disintegrant. However, it needs further developments to increase the profiles, such as strong bonds within the intermolecular of the starch during compression and faster in water absorption (swelling) to gain faster disintegration time.

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