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Research Article

PREPARATION AND CHARACTERIZATION OF PRAGELATINIZED CASSAVA STARCH PHTHALATE AS A PH-SENSITIVE POLYMER FOR ENTERIC COATED TABLET FORMULATION

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ABSTRACT

Modification of starch is a process which intended to expand utilization of starch as pharmaceutical excipients. In the present study, pragelatinized cassava starch phthalate (PCSPh) was produced by a process of pregelatinization of cassava starch and then esterification using phathlic anhydride in basic aqueous medium. The obtained PCSPh was characterized, including degree of substitution (DS), functional group, thermal properties and solubility. PCSPh was then utilized as coating material for tablet using ketoprofen as drug model. Core tablets were prepared by wet granulation process and then compressed into white round-biconvex tablets. Subsequently, core tablets were coated with coating solution, containing PCSPh 5%. The results showed that PCSPh possess DS of 0.054; carbonyl ester was detected at infrared wavenumber of 1716.70 cm^{-1}; melting temperature at 156.52 – 164.48 ^{o}C and lower solubility in acid medium rather than in base medium. The coated tablets possessed good appearance, hardness and friability. Moreover, coated tablets were undisintegrated in acid medium for 1 hour, and the dissolution of ketoprofen from coated tablets were less than 10% in acid medium (pH 1.2). The results revealed that PCSPh was prospective to be applied as a enteric polymer excipient for enteric-coated tablets.

Keywords: Cassava starch, Pragelatinized cassava starch phthalate, pH-sensitive polymer, Enteric coated tablet

INTRODUCTION

Due to its low price and abundant availability, native starch is widely used for pharmaceutical excipient as tablet filler, binder and disintegrant (1). However, the use of native starch as film-forming excipient is still limited due to its physical properties. There are several strategies to improve properties of cassava starch, including physical, chemical and enzymatic modification (2).

Gelatinization process, one kind of physical modification of starch, could produce pragelatinized starch with better flowability and solubility in cold water. Physical modification of starch can be also combined with chemical reactions to change functional properties of the starch. Esterification reaction between hydroxyl group of starch and carboxylic group of acid or derivatives (anhydride, acyl chloride, etc) is one kind of chemical modification. Esterification reaction can be performed in aqueous medium and organic medium (3, 4, 5).

Thakore, Desai, Sarawade, & Devi has shown that starch esterification using phthalic anhydride can improve film forming ability of starch (6). Therefore, starch phthalate potentially be used as coating materials, especially for enteric coated dosage forms to retain release of the drug in stomach so that can either protect unstable drug from hydrolized at acid condition or the gastric mucosa from irritating drugs.

In this study, cassava starch was physically and chemically modified by gelatinization and esterification process in an aqueous-base medium (pH 8-9) using phthalic anhydride. The obtained pragelatinized cassava starch phthalate (PCSPh) was then used as coating material for enteric-coated tablets. Ketoprofen, a nonsteroidal anti-inflammatory drugs (NSAID), was used as drug model in this study for its side effect on irritating stomach which cause nausea and gastritic.

MATERIALS AND METHODS

Materials

Cassava starch (Sungai Budi Lampung, Indonesia), phthalic anhydride (Merck, Germany), ethanol 96% (Merck, Germany), sodium sulphate anhydrous (Merck, Germany), polyethylenglycol 400, glyserol (Brataco, Indonesia), ketoprofen (kindly gifted by Sanofi Aventis, France), talcum (Haichin, China), Avicel®PH 101 (Mingtai Chemical, China), Primogel® (DMW International, Deutch), povidone (BASF Chemical Company, Germany), hydroxypropyl methyl cellulose phthalate (Shin-Etsu Chemical, Japan).

Methods

Synthesis of Pragelatinized Cassava Starch Phthalate

In this study, pragelatinized cassava starch phthalate was obtained from two steps: gelatinization and esterification. Gelatinization process was performed by heating starch solution above 70°C and drying it into flakes which were then milled and sieved. The obtained pragelatinized cassava starch powder was then dispersed in purified water and reacted with solution of phthalic anhydride in ethanol 96%. Solution NaOH 10 N was continously dropped during reaction to keep alkaline condition in pH 8-10. Sodium sulphate anhydrous was also added during reaction to absorb the execive water. Reaction was conducted under 1000 rpm stirring speed of homogenizer. The stirring was continued until 30 minutes after reaction was completed and the solution was allowed to stand overnight. The solution was then neutralized by adding HCl solution to reach pH 6.5 – 7.

Ethanol 50% solution was added into neutralized solution to wash the excesive unreacted phthalte. Phthalate residue was detected by spectrophotometer UV-Vis. The obtained precipitate was then dried, milled and sieved to obtain PCSPh powder.

Characterization of PCSPh

Physical Characterization

Physical characterization on PCSPh include its morphology, thermal properties, powder flowability, moisture content, hygroscopicity and solubility. The shape and morphology of the PCSPh powders were observed with a Scanning Electron Microscope (SEM). Thermal analysis was carried out using Differential Scanning Calorimeter (DSC) at temperature of 30°C to 500°C. Moisture content was measured by moisture balance using 1 gram of sample powder which heated at temperature of 105°C. Hygroscopicity test conducted on 1 g sample PCSPh which placed in a desiccator at room temperature and humidity of 70% RH. The sample is placed in four different containers. PCSPh weight changes before and after treatment were recorded. Solubility test performed by dissolving 250 mg PCSPh in several solvents with different pH (pH 1.2 and pH

5; distilled water; phosphate buffer at pH 7.4; NaOH solution of pH 10 and pH 12 with 1 N NaOH). Solubility of PCSPh was calculated by measuring dissolved phtalate using UV-Vis spectrophotometer at isobestic wavelength (255 nm).

Chemical Characterization

Chemical characterization of PCSPh was conducted on its degree of acidity, functional groups and degree of substitution. Acidity is measured by dissolving PCSPh in distilled water with a concentration of 10% then the pH was measured using a pH meter. Subtitution of phthalic groups in starch was ascertained by infrared spectrophotometer. IR spectra of PCSPh was compared to PPS. Phtalic groups showed a specific absorption ester bonds at wave numbers 1710-1750 cm^{-1}. The degree of substitution was measured using UV-Vis spectrophotometer. About 50 mg PCSPh was dissolved in 1.0 N NaOH solution, and the phthalic absorbance was measured at a wavelength of 271.8 nm. Degree of phthalic subtitution in PCSPh was calculated using equation below (2):

$$\text{Degree of phthalic subtitution} = \frac{162 \text{ x \% phthalic}}{14.900 - (148 \text{ x \% phthalic})}$$

Functional Characterization

Functional characterizations were conducted on the flow properties of PCSPh powders, viscosity and rheology of PCSPh solution, swelling index and gel strength. The flow properties of PCSPh powder were measured toward flow rate, angle of repose, Hausner ratio and compressibility index. Viscosity and rheology was performed on PCSPh solution with a concentration of 3, 5, 7 and 10% w/v using Brookfield viscometer. Swelling index was performed by comparing the weight of dry tablet of PCSPh and the weight after been placed in 10 mL medium in different pH. Gel strength was measured using texture analyzer on solid gel of 10% PCSPh which has been cooled at a temperature of ± 4°C for 2 hours.

Formulation of Ketoprofen Enteric Coated Tablet

Core tablets were prepared by wet granulation method using 5% solution of PVP as a binder. Wet granules was dried and characterized then compressed into white-round-biconvex tablets with a diameter of 9.1mm.

Table 1: Formulation of Ketoprofen Core Tablets

Formulation	Each Tablet (mg)	Each Batch (gram)
Ketoprofen	100	40
Avicel PH 101	180.5	72.2
Primogel	9	3.6
PVP	6	2.4
Talcum	3	1.2
Magnesium stearat	1.5	0.6

Core tablets were coated by coating solution, using pan coating method with optimized coating parameter. Polyethylenglicol 400 and glyserol were added into coating solution as plasticizer. HPMCP was used as additional coating material.

Table 2: Formulation of Coating Solution

Formula	F1	F2	F3
PCSPh (g)	5	4	3
HPMCP (g)	-	1	2
Glyserol (g)	1.5	1.5	1.5
PEG 400 (g)	1	1	1
Aquadest ad (mL)	100	-	-
NH_4OH 0.03% ad (mL)	-	100	100

Evaluation of Ketoprofen Enteric Coated Tablet

Organoleptic evaluation were visually performed on core and coated tablets including appearances (color and shape) and the presence of physical defect. Size uniformity was evaluated on 20 tablets by measuring diameter and thickness of the tablets. Weight uniformity test was carried out by weighing 20 tablets using analytical balance. Hardness of tablets was measured using hardness tester while the friability using friabilator at 25 rpm of speed for 4 minutes. Assay of ketoprofen in tablet was evaluated by dissolving the tablets in phosphate buffer medium pH 7.4 then the absorption was measured using UV-Vis spectrophotometer at a wavelength of 260 nm.

Disintegration of tablet was tested using disintegrating tester. Core tablets should be disintegrated in 37°± 0.5° C distilled water medium in 15 minutes while enteric coated should not be disintegrated in 900 ml HCl 0.1 N medium 37°± 0.5° C for 1 hour but should be disintegrated when the test was continued in phosphate bufferpH 7.4 medium 37°± 0.5° C for 15 minutes.

Release profile of ketoprofen from coated tablets was studied using dissolution tester in 900 ml HCl 0.1 N medium 37°± 0.5° C for 2 hours and continued in phosphate buffer pH 7.4 medium 37°± 0.5°C for 45 minutes. The released drug was measured using UV-Vis spectrophotomete rat a wavelength of 260 nm. Enteric coated tablets should not release the drug more than 10% in 2 hours in acid medium and should release the drug over 85% in 45 minutes in pH 7.4 phosphate buffer medium (7).

RESULTS AND DISCUSSION

Synthesis of Pragelatinized Cassava Starch Phthalate

Synthesis of pragelatinized cassava starch phthalate (PCSPh) was conducted in two steps, gelatinization and esterification step. Cassava starch powder was dispersed in distilled water and heated above 75°C and the obtained starch paste was then dried using drum drier at temperature of 80±5°C. During this process, starch granules swells rapidly, absorbing water in large quantities into the granules and causing rupture. Rupture of starch granules are irreversible. The obtained PCS was then milled using disc mill and sieved through 60 mesh siever. Esterification reaction was carried out by reacting 10% PCS mucilago in distilled water with 16.7% solution phthalic anhydride in ethanol 96%. Conditions of the reaction was maintained at pH 8-10 by addition of 10N NaOH solution continuously. In alkaline conditions, the hydroxyl group of starch will be ionized and could react with carboxylic groups. In aqueous medium, the reactivity of acid anhydride decrease since it turns into a carboxylic acid. In order to minimize water content in the reaction, sodium sulphate anhydrous was added during reaction to absorb water molecules obtained from esterification.

Reaction was conducted under 1000 rpm stirring speed of homogenizer. The stirring was continued until 30 minutes after reaction was completed and the solution was allowed to stand overnight. Esterification reaction is considered complete if there is no change in pH in the solution of the synthesis results. The solution was then neutralized by adding HCl solution to reach pH 6.5 – 7.

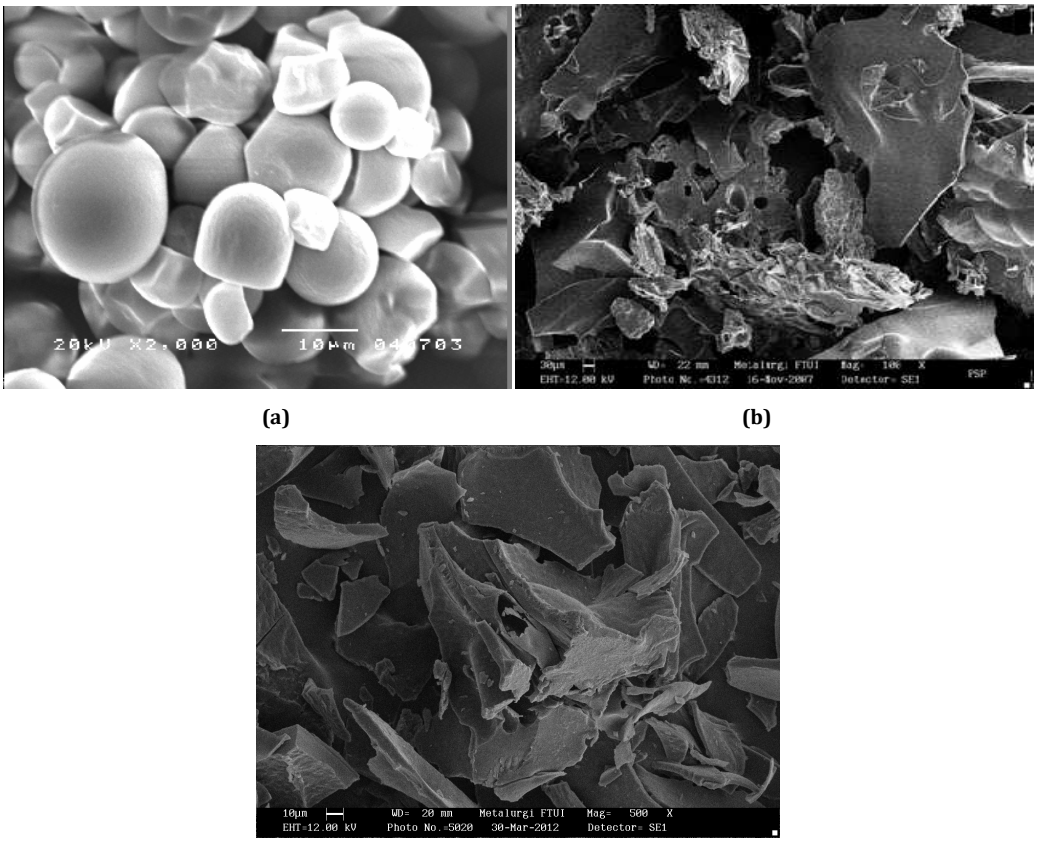
Ethanol 50% solution was added into neutralized PCSPh to form a white precipitate. The precipitate was then washed with 50% ethanol until no phthalates detected in the last rinse (identified by the absence of absorption or peak in UV-Vis spectrophotometry at a wavelength of 280 nm). The precipitate was dried using a drum drier at a temperature of 80 ± 5°C, milled using disc mill and sieved through a 60 mesh siever to obtain PCSPh.

Characterization of Pragelatinized Cassava Starch Phthalate

Physical and Morphological Properties

The obtained PCSPh was an odorless and yellowish-white fine powder. Two steps of drying process which used in manufacture of PCSPh contributing in yellowish color of PCSPh powder, compared to white-color of cassava starch. PCSPh was also more voluminous than PCS, supported by density data of PCSPh and PCS powder.

Observation on morphology of the cassava starch, PCS and PCSPh was performed using scanning electron microscope (SEM). Figure 1 shows that cassava starch possessed round-shaped of granules while PCS and PCSPh had irregular-shaped of flakes. This shape of powder was due to drying process using a double drum drier that break the granule of starch and turn it into irregular thin flakes form.



(a) **(b)**

(c)

Fig. 1: SEM Micrograph of (a) cassava stach (100x magnification), (b) PCS (500x magnification), (c) PCSPh (500x magnification)

pH of PCSPh

Measurement of pH of the samples were performed on solution of 5% in distilled water. The results showed that pH of 5% solution of PCSPh was 5.72±0.11,while pH of 5% solution of PCS was 6.69±0.32. There were significant differences between pH of PCS and PCSPh. The presence of free carboxylic acid in PCSPh resulted in more acidic solution.

Degree of Subtitution (DS)

The amount of phthalate substituted in starch was measured using UV-Vis spectrophotometer at a wavelength of 271.8 nm. Sample solution was prepared by dissolving PCSPh powder in a solution of NaOH 1N to form a clear solution which was assumed that all phthalates were perfectly dissolved and can be detected by UV-Vis spectrophotometer. Phthalate concentration in the sample solution was then calculated by plotting the absorbance of solution into calibration curve equation of potassium hydrogen phthalate.

Phthalate levels of 4.74 ± 0.16% equivalent to the value of the degree of substitution of 0.0541 ± 0.00186. This means there are about five groups were substituted phthalates in PCS per 100 anhydroglucose units. Substitution of phthalates is estimated to occur in starch reactive groups of hydroxy at C position 2, 3, and 6, with the greatest possibility of substitution at position C-2 because of the great reactivity (8).

The degree of substitution PCSPh of 0.0541 was obtained from the reaction of 50% phthalic anhydride. Compared to aliphatic substitution groups such as acetate or propionate, phthalate substitution on PCS generate the smallest degree of substitution. This may be caused by the larger aromatic shape of phthalate, compared to aliphatic groups, therefore it was more difficult to penetrate into the structure of starch molecules (8).

The degree of substitution affect functional properties of PCSPh, especially solubility. The higher the degree of subtitution, the lower the solubility in acidic medium. Phthalate grups in starch molecules can only be ionized and dissolved in alkaline conditions. This property allows PCSPh to be used to retain the drug release in the stomach.

Functional Group Analysis

Analysis of functional groups on PCSPh was performed using an infrared spectrophotometer to ensure the phthalates substitution in PCS. Figure 2 shows the difference spectrum of PCS and PCSPh at wavenumbers of 1500 to 1700 cm^{-1}. Figure 2 explains the differencies of absorption bandwith between PCS and PCSPh spectrum. PCSPh possessed peak with weak intensity at a wavelength of 1716.70 cm^{-1} which indicates the carbonyl group (C = O) of ester compound. The peak indicate the presence of phthalate esters in the starch.

Thermal Analysis

Thermal properties of starch, PCS and PCSPh were analyzed using differential scanning calorimeter (DSC). Endothermic curve which was shown as decline curve (Figure 3 and Table 3) shows the differencies between cassava starch, PCS and PCSPh. Endothermic process usually occurs in the process of changing the phase of a substance, such as melting process. Endothermic process is characterized by a negative energy value, which means that the melting process absorbs heat energy. Thermal energy were required by the sample to change its form from solid to liquid. Figure 3 shows that cassava starch has a wider melting range and absorb more heat energy than PCS and PCSPh. This is because cassava starch requires greater heat energy to break its granule shape before turned it into liquid form, while PCS and PCSPh only absorb lower heat energy since there were no granules to be brokendown. Table 3 also shows that the melting temperature of PCSPh was higher than the melting temperature of cassava starch and PPS. Phthalate substitution on starch causing higher molecular weight of PCSPh which require higher temperature to melt the powder.

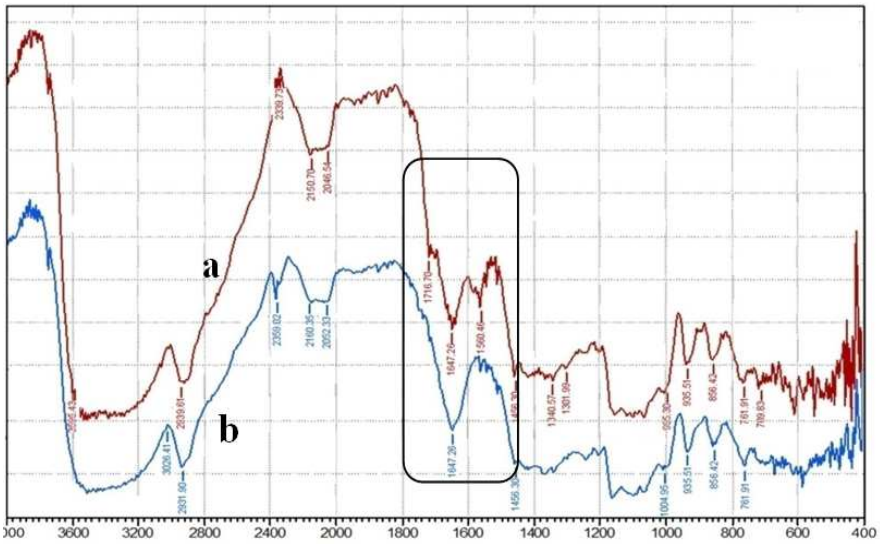


Fig. 2: Infrared Spectrum of (a) PCSPh dan (b) PCS

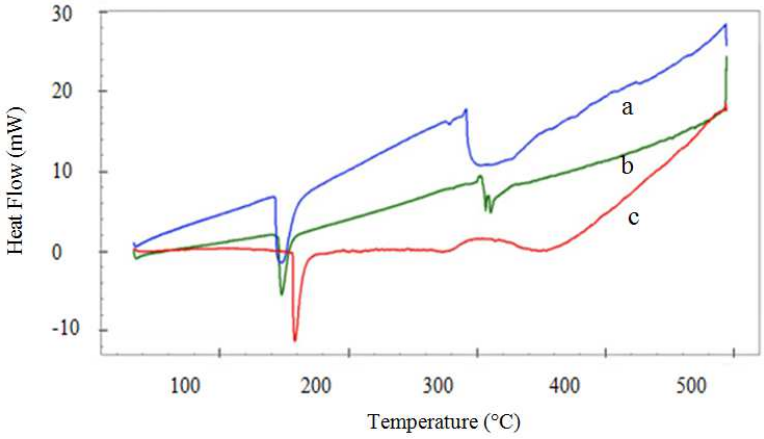


Fig. 3: Endotermic Curve of (a) cassava starch, (b) PCS dan (c) PCSPh

Table 3: Comparison of endothermic curve of cassaca stach, PCS and PCSPh powder

Parameter	PCSPh	PCS	Cassava Starch
Melting Range (°C)	156.52 – 164.48	145.18 – 153.96	143.45 – 158.55
Melting Enthalpy (J/g)	- 100.78	- 105.06	-156.48

Moisture Content and Hygroscopicity

Moisture content was determined by drying the sample at temperature of 105°C using a moisture balance. Cassava starch and PPS has a high water content (5-12%) eventhough the value still meet Pharmacopoeia specification, which is less than 16% for cassava starch and less than 14% for PCS (9). Moisture content of a powder are related to its flow properties. High water content in a powder increase the adhesion force between particles which can cause poor flow rate of an excipient (10).

Measurements of moisture content showed that the moisture content of PCSPh was lower (5.76% ± 0.060%) than that of PCS (11.31% ± 0.221%). This may be related to washing process of PCSPh, which use 50% ethanol that evaporated easily during drying process and left slightly water within dry powder PCSPh. The low moisture content in PCSPh powders improved the flow rate of PCSPh (11.53 ± 2.20 g/sec), compared to PCS's flow rate (1.95 ± 0.38 g/sec). Native starch had hygroscopic properties and readily absorbs moisture from the air (9). Therefore, determination of hygroscopicity of starch and its derivatives is important to determine appropriate storage conditions to reduce the excessive absorption of moisture by the starch.

Figure 4 shows that the samples which were stored in a closed container with silica gel had the lowest percentage of weight increase. It shows that starch and its derivates should be stored in a tightly sealed container with silica gel. PCSPh powder absorbed more moisture, compared to PCS (Figure 4). PCSPh powder contains very small of water, and there are many hydroxyl groups in structure to allow more water absorption. The low water content in PCSPh give higher ability to absorb moisture from the air. Therefore the higroscopicity of PCSPh was higher than PCS and native cassava starch.

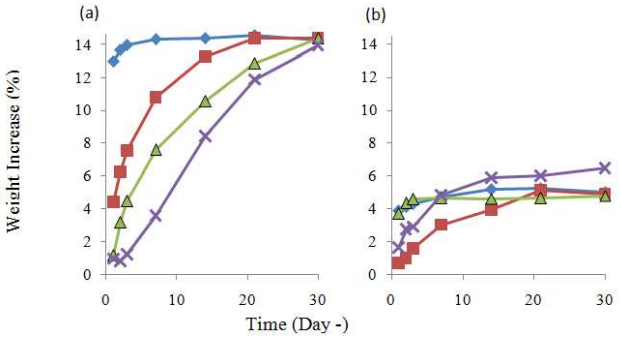


Fig. 4: Hygroscopicity of (a) PCSPh and (b) PCS in different storage condition; (♦) unsealed container, (■) sealed container, (▲) unsealed container without silica gel, and (X) sealed container wtih silica gel

Solubility

The term of solubility which used in this research were calculated from the amount of phthalates that are dissolved in several medium with varying pH. Determination of concentration of phthalates which were dissolved performed using UV-Vis spectrophotometer at isobestic wavelength of phthalate (255 nm).

Qualitatively, PCSPh in alkaline solution showed more clearly solution than in acid medium, which indicated that PCSPh was more soluble in alkaline medium rather than in acidic medium. Figure 5 shows the solubility of PCSPh in various medium pH's, which was increasing as the pH medium was increased. There were significant differences between solubility of PCSPh in acidic medium (pH 1.2) compared to its solubility in alkaline medium (NaOH 1 N). The higher substituted phthalate on the starch, the easier to be ionized and dissolved in alkaline medium, the more clear the solution. In accordance with the results showed in Figure 5, PCSPh can be indicated as a prospective excipient to be used as an enteric excipient to to retain drug release in the stomach.

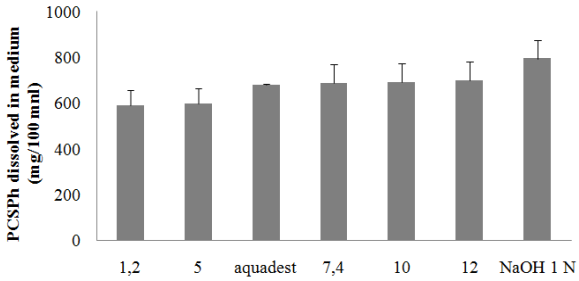


Fig. 5: Solubility of PCSPh in several medium with varying pH

Gel Strenght

Gel strength of samples were measured on samples which already prepared in solid gel form of 10% PCSPh and also PCS. PCSPh showed greater gel strength (31.90 ±2.17 gf) than PCS (12.64 ±1.30 gf). This property might be correlated to swelling index. The crosslink structure caused PCSPh possessed lower swelling index, but yet showed greater gel strenght. These properties might allow the application of PCSPh as matrix for sustained-release dosage forms.

Swelling Index

Swelling index of excipient in a medium will affect the drug release from dosage forms. Swelling index were calculated from weight increase of PCSPh tablets in several medium. Figure 6 shows that in the first five minutes, PCSPh were rapidly swelled in alkaline medium (pH 7.4), but for the rest time of test, swelling index of PCSPh in acidic and alkaline medium showed no significant differencies. Figure 6 and Figure 7 shows that the swelling index of PCSPh was lower than PCS. It indicates that PCSPh prospectively to be used in retaining drug release from dosage forms. Figure 7 also shows that in the acidic medium, the swelling index of PCSPh were lower than PCS. This result shows that the ability of PCS to expand its structure changes when it was reacted with phthalic group. This could be predicted that the reaction between phthalate groups and starch were not only substitution reaction but also crosslinking reaction that cause the decrease of swelling index of starch. The presence of the crosslink structure decrease the ability of water to penetrate into the structure of amylose and amylopectin. Based on these results, PCSPh are potentially be used as excipients for the controlled release dosage forms.

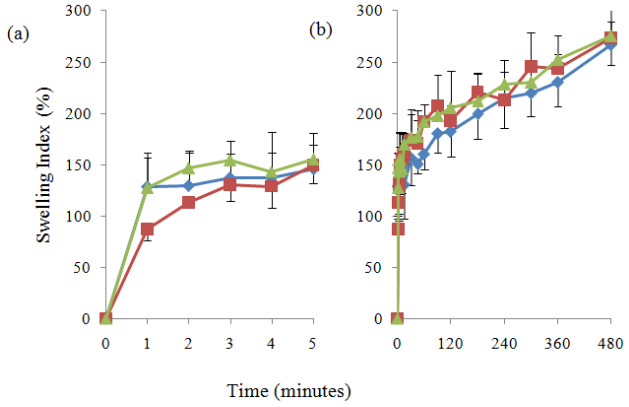


Fig. 6: Swelling index of PCSPh in (♦) HCl pH 1.2 medium, (■) aquadest dan (▲) phosphate medium pH 7.4 for (a) 5 minutes dan (b) 480 minutes

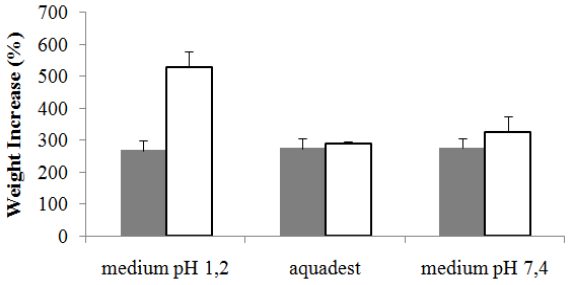


Fig. 7: Swelling index of PCSPh (■) and PCS (□) after 8 hours

Viscosity and Rheology

Viscosity and rheological properties were performed to optimize concentration of PCSPh solution to obtain good film coating solution and homogenous coating layer on tablets. Viscosity of PCSPh was evaluated using the Brookfield viscometer at concentration of 3%, 5%, 7%, and 10%. Viscosity value of PCSPh and PCS were shown on Table 4. The results show that increasing PCSPh concentration increased its viscosity. Due to the hydrophilic properties, PCSPh swelled and formed colloidal solution when were dispersed in water. Therefore, increasing amount of polymer increases the viscosity.

Comparing PCS to PCSPh's viscosity at the equal concentration, it shows that PCS was more viscous than PCSPh. This phenomena could be related to alteration of network structure of PCS when modified into PCSPh, thus not allowed the water to penetrate as easier as PCS. This phenomena lead to the lower viscosity of PCSPh dispersion solution.

Table 4: Viscosity of PCS and PCSPh

Rate (rpm)	Viscosity (cps)				
	PCSPh 3%	PCSPh 5%	PCSPh 7%	PCSPh 10%	PCS 5%
0.5	800	2800	11200	172000	4400
1	500	2100	7600	108000	3200
2	300	1500	5000	67000	2200
2.5	280	1360	4480	56800	1920
5	180	980	3040	36000	1440
10	120	710	2080	23000	1080
20	95	525	1480	14800	800
10	120	690	2000	22000	1080
5	180	940	2880	33600	1440
2.5	280	1320	4160	53600	1920
2	300	1450	4800	64000	2200
1	500	2100	7200	104000	3200
0.5	800	3000	11200	168000	4800

There are significant differences between rheology of PCS and PCSPh. Figure 9 shows that the 5% PCS solution in distilled water possessed pseudoplastic properties. As the rate of share increase, the viscosity of solution decrease. As the shearing stress increase, PCS molecules would arranged in the direction of flow, so that the viscosity of solution will decrease. Similiar to the 5% PCS solution, the 3% PCSPh solution had pseudoplastic properties, but with increasing concentrations of PCSPh, the properties of solution changed. Solution of 5%, 7% and 10% of PCSPh possessed pseudoplastic-ticsotropic properties.

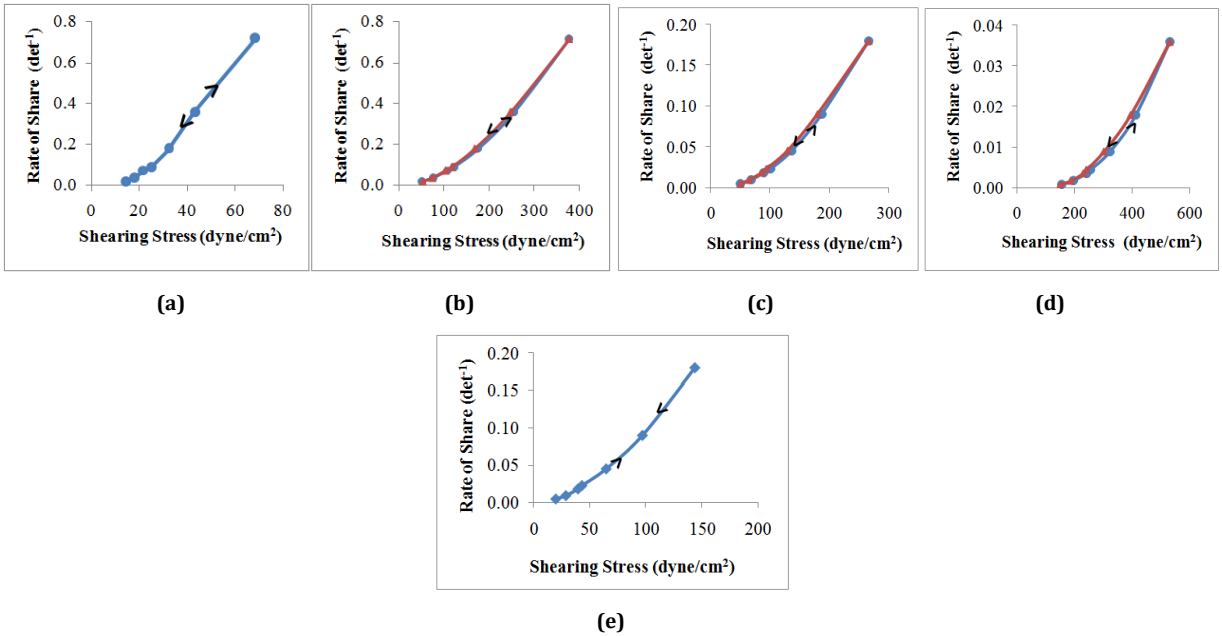


Fig. 8: Rheogram (a) PCSPh 3% ; (b) PCSPh 5% ; (c) PCSPh 7% ; (d) PCSPh 10% and (e) PCS 5% solution in distilled water

Formulation and Evaluation of Ketoprofen Enteric Coated Tablet

Core tablets were prepared by wet granulation method using 5% PVP solution as binder. Wet granules was then dried and characterized. The result shows good flow rate which contribute on weight uniformity of tablets. Dried granules were then compressed into white-round-biconvex tablets with a diameter of 9.1 mm.

Table 5: Flowability of ketoprofen granules

Parameter	Results
Flow rate	8.01 ± 0.15 gram/sec
Angle of repose	39.37 ± 0.59 ° (poor)
Hausner Ratio	1.310 ± 0.03 (fair)
Carr Index	23.67 ± 1.53 (fair)

Core tablets prepared by compressing the granules using Korsch Tabletting Machine, resulting white-round biconvex tablets. This biconvex shape is suitable as core tablets since its free-flowing properties in coating pan. Usage of PVP as binder solution produce tablets which posses high hardness and very low friability (<0.1%). This is good characteristic for tablet to be coated, as shown at Table 6. Although the core tablets possess high hardness properties, but it was disintegrated less than 15 minutes in distilled water. Thus, the characteristics comply to the the requirements of Pharmacopoeia.

Table 6: Characteristic of Core Tablets

Parameter	Results
Weight	300.54 ± 1.69 mg (RSD = 0.56%)
Hardness	24.87 ± 1.572 Kp
Friability	0.092%
Disintegration time	6.57 ± 0.72 menit
Assay	98.31 ± 3.68 %

The core tablet was coated with three different coating solution formulas. PCSPh 5% solution in distilled water was a coating

formula 1, while mixed solution of PCSPh-HPMCP at ratio 4:1 and 3:2 were the coating formula 2 and 3, respectively. HPMCP was used as combination with PCSPh to improve the retardation of drug release through coating layer in acid medium. NH_4OH 0.03% was used to obtain homogeneous HPMCP and PCSPh solution. Since heat above 60-70 °C during coating process cause decomposition of NH_4OH into evaporated NH_3, it could be concluded that there were no excesive NH_4OH left on the tablets. Plasticizer, containing glycerol and PEG 400, was added into coating formula to form strong and elastic film layer.

Table 7: Evaluation Result of Core Tablet and Coated Tablet

Parameter	Core Tablet	Coated Tablet		
		F1	F2	F3
Weight (mg)	300.54 ± 1.69	317.81 ± 1.37	317.62 ± 1.31	318.32 ± 1.24
Thickness (mm)	4.74 ± 0.03	4.82 ± 0.02	4.83 ± 0.02	4.88 ± 0.03
Hardness (kP)	24.87 ± 1.57	28.90 ± 1.66	28.56 ± 1.52	29.66 ± 1.56
Weight Gain (%)	-	5.75	5.68	5.92
Friability (%)	0.092	0	0	0
Disintegration time (minutes)				
- aquadest	6.57 ± 0.72			
- HCl		One tablet was disintegrated on 50 min 12 sec	Six tablets remain	Six tablets remain
- Phosphate buffer pH 7.4				
		10.80 ± 2.7	6.67 ± 0.91	4.7 ± 0.7

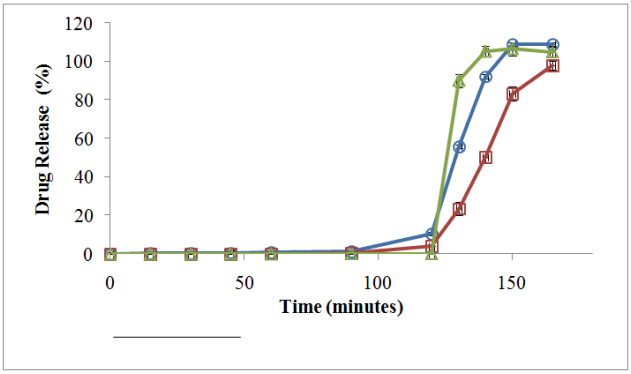


Fig. 9: Release profiles of ketoprofen from enteric coated tablet F1 (○), F2 (□), dan F3 (△) for 2 hours in acid medium pH 1.2 and continued for 45 minutes in phosphate buffer medium pH 7.4

Core tablets were coated with three formulas of coating solution until the weight gain of tablets were up to 6%. Table 7 shows that all of six coated tablets of F2 and F3, as well as five of six coated tablet F1, were not disintegrated in acid medium for 1 hour, while one of six tablet from coated tablet F1 were disintegrated in 50 minutes. All of coated tablet were immediately disintegrated in phosphate buffer medium in 5 minutes.

Figure 9 shows that all coating formula was able to retain the drug release from coated tablet in acid medium. However, F1 formula (PCSPh 5%) release of active substances greater than 10% (10.48 ± 1.3%) in acid medium. This means that the tablet F1 did not comply the requirement as enteric-coated tablets. However, tablets which are coated with coating formula F2 (PCSPh-HPMCP 4:1) and F3 (PCSPh-HPMCP 3:2) shows ability to retain drug release in the acidic medium. This phenomena was due to HPMCP containing in F2 and F3 coating formula. HPMCP contains more phtalic group (33.2%) than PCSPh (4.7%). The more phthalic group contained in excipient, the more difficult this excipient to be ionized in acidic medium. At medium pH 1.2, HPMCP can not be dissolved so it can retain the release of ketoprofen. Drug release in acid medium was significantly decreased by increasing HPMCP concentration in coating solution formula.

In contrary, ketoprofen was immediately released from coated tablets when they were moved into alkaline medium. In alkaline medium, the phthalic group was ionized, thus the coating film layer would be dissolved. When the coating layer was dissolved in the dissolution medium, water would absorbed into the tablets and causing disintegration of tablets. Since the tablet disintegrated, the active ingredient in the tablets could be dissolved in the medium. At the end of dissolution test in base medium, ketoprofen have been released more than 80% from the tablets which coated with all formula of coating solution. The results reveal compliance with the requirements for enteric-coated tablets. Therefore PCSPh could be used as an enteric coating material. Based on the obtained results, it is expected to increase the weight by more than 6% of the PCSPh can be used as a single excipient for the tablet enteric coating.

CONCLUSION

1. Cassava starch has been successfully modified through gelatinization and esterification with phthalic acid anhydride in alkaline aqueous medium to produce pragelatinized cassava starch phthalate (PCSPh) with a degree of substitution (DS) of 0.0541.

2. The obtained PCSPh were more soluble in alkaline medium than in acidic medium, thus it might be used as a tablet enteric coating excipient for enteric tablets.

3. PCSPh combined with HPMCP by the ratio of 4:1 has been successfully used as an excipient coating for enteric-coated tablet and able to delay the release of ketoprofen in acid medium.

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