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An Approach on Pregelatinized Cassava Starch Phosphate Esters as Hydrophilic Polymer Excipient for Controlled Release Tablet

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This study describes a new approach on pregelatinized cassava starch phosphate as hydrophilic polymer excipient for controlled released tablet. There are two classes of starch phosphate esters, substituted starch phosphate esters dan cross linked starch esters. First, pregelatinized cassava starch was phosphorylated by adding phosphorous oxychloride ($POCl_3$) for making cross-linked reaction (CPCS). Secondly, pregelatinized cassava starch was phosphorylated by adding sodium monohydrogen phosphate (Na_2HPO_4) for making substituted reaction (PCSN). Both pregelatinized starch phosphates subsequently were used as hydrophilic polymer matrix tablet controlled release with various concentrations. The tablets were prepared separately by directing compression process and theophyline was used as a model of the active ingredient. The USP Basket was selected to perform the dissolution test of the tablets, which carried out separately in 0.1 N HCl (pH 1.8) and in phosphate buffer of pH 7.2 both for 3 h. The result of these studies indicated that CPCS and PCSN were suitable material for the matrix tablet controlled release at 30-50% w/w concentration of theophylline. The release profiles all of the drugs were follow zero-order kinetics. The highest polymeric concentration of CPCS (50% w/w) indicated the slowest rate of drug release. The drug release from all tablets may be controlled by combination of diffusion and erosion delivery system. The pregelatinized cassava starch phosphate CPCS was more reasonable than PCSN for controlled release tablet dosages form as hydrophilic polymer excipient.

Key words: Pregelatinized starch phosphate, hydrophilic polymers excipient

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INTRODUCTION

Natural starch has been recognized as one of the most commonly used excipients in the manufacturing of tablets as fillers and disintegrants (Wade and Weller, 2000). However, due to their limitations, untreated or natural starches are poor in compressibility, flow properties and not able to swell in cold water. Some special starch products, such as pregelatinized starch were developed (Bos *et al*., 1992). Pregelatinized starch has been made by mechanically processed to rupture all or part of the granules in the presence of water and subsequently dried. The compounds in starch granules are amylose, amylopectin and others that leach out all or part from the granules when the granule ruptured. There are two classes of pregelatinized starches, fully and partially pregelatinized starches.

Partially pregelatinized starch contains soluble (gelatinized) and insoluble fraction, that are normally use as binder-disintegrants in immediate release tablet formulations (Wade and Weller, 2000; Cunningham, 1999). Physically modified starch, such as thermally modified starch has been used for controlled drug release (Rak *et al*., 1983; Van Aerde and Remon, 1988). Fully pregelatinized starch is extremely soluble in cold water, eliminating the need to prepare heated starch for wet granulation application. These materials have a very limited obstructive gel formation capability at tablet surface (Leach *et al*., 1959), which make them not particularly suitable for sustained release applications. Making them phosphate esters causes the material characteristics changing, particularly, gel formation.

Chemical modified of starch, such as phosphate derived, has two groups, substituted as mono-ester and cross-linked starch phosphate esters as di- or three-phosphates. These products are not able to increase viscosity and gel formation in cold water, therefore they can not be considered as a matrix material for controlled or sustained release tablet. Pregelatinized starch phosphate possibly can be used as polymeric hydrophylic material to control the drug release, because of they can improve the functional properties, swelling in cold water for gel formation.

The ester phosphate groups are bound to the C position of glucose units of amylopectin molecules in untreated natural starch. Based on isolable phosphorylated residues starch, 28% of the phosphate groups were bound in C-2 position, 9% were bound at C-3 and 63% were bound at C-6 (Solarek, 1989; Tobata and Hiruzuki, 1971). The position of phosphate groups in pregelatinized starch phosphate possibly are same with untreated starch at amylopectin fraction.

Preparation of pregelatinized cassava starch phosphate cross-linking can be made by reacting pregelatinized cassava starch with $POCl_3$, to produce phosphate di-ester, bound at C-3 and C-6 position on the same polymer chain in molecule or different hydroxyl groups on other molecules and built between branches of the amylopectin molecules (Solarek, 1989; Wurzburg, 1989). Both of them are able to swell in the present of water and forming a gel-like consistency substance. This properties make them suitable as hydrophilic polymer matrix in controlled release tablet, like previous reported, pregelatinized marantha starch phosphate substituted that was prepared by reacting the pregelatinized starch with Na_2HPO_4 and $NaHPO_4$ (2;3) proved as hydrophilic polymer matrix (Effionora *et al*., 2006).

The controlled release drug needs a suitable hydrophilic polymer, which is able to swell in the present of water and forming a substance with a gel-like consistency. The release behaviors of drugs depend on type of the matrix, capability of swelling, diffusion and erosion process (Colombo *et al*., 1995; Sung *et al*., 1996; Siepman *et al*., 1999). Among hydrophilic polymers, derived polysaccharides are the best choice material due to their safety and acceptance (Bonferoni *et al*., 1993). Some of the derived polymers are cellulose ethers (Ford *et al*., 1987), tamarind seed polysaccharide (Sumanthy and Ray, 2002) and xanthan gum (Tadukdar and Plaizer-Vecammen, 1993).

This study reports a study on the capability of CPCS and PCSN as controlled-release matrices. Theophylline is used as a model active compound in the tablet, because it has a very narrow therapeutic range (Shangraw, 1988; Geresh *et al*., 2004). Further more, cassava as raw material to produce pregelatinized starch is inexpensive and available abundantly in many tropical countries especially Indonesia.

MATERIALS AND METHODS

Materials: Materials used in this study were Cassava starch (PT. Sungai Budi Industry, Indonesia), Theophyline (Hunan Pharmaceutical Factory, Hongkong), $POCl_3$, Na_2HPO_4, Na OH and HCl (Merck Chemical Co., Germany), Magnesium stearate, Talc and Stearic Acid (Takehara, Kagaku Kogyo Co Ltd., Japan) and Lactose Spray Dried (DMV International).

Preparation of pregelatinized cassava starch: A suspension consisting of 35% cassava starch in water was dried in a double drum dryer at 80±5°C. The dried product was pulverized and sieved with mesh 100.

Phosphorylation pregelatinized cassava starch: Both CPCS and PCSN were prepared by suspending pregelatinized starch in an aqueous alkaline (pH 9.0-10.0) by adding 5 N NaOH. CPCS was then phosphorylated using 0.5% $POCl_3$, while PCSN used 0.3% Na_2HPO_4. The temperature of both reactions was maintained at room temperature. After 2 h, the pH of the suspension was adjusted to 6.5 with 1 N HCl. CPCS and PCSN were then dried in oven at 40°C and double drum dryer at temperature 80±5°C, respectively. Finally, the dried products were pulverized and sieved with mesh 100.

Physico-chemical properties of pregelatinized starch phosphate: The samples were determined, moisture content, density (bulk), density (tapped), residue of ignition, pH, flow rate, angle of ripose and compressibility index.

The particle shape of the pregelatinized starch and pregelatinized starch phosphate: The particle shape was determined using a scanning electron microscope JEOL 5310 LV, Japan. Gold (Au) was used to coat the tablet using vacuum evaporator S 500. After attached starch on a holder of the vacuum by specific glue, the holder was put in to the instrument to see the shape of the particle compound.

Viscosity: Pregelatinized cassava starch, CPCS and PCSN were dispersed in water at concentration 5% w/v. Viscosity of the materials were analyzed by using Viscometer Brookfield, Synchrolectric, USA.

Gel forming: Pregelatinized cassava starch, CPCS and PCSN were dispersed in water at concentration 15% w/v. The gels strength were measured by using Penetrometer Water Herzog GmbH, Germany.

Preparation and characterization matrix tablet: The compositions of tablet matrix formulation were listed in Table 1. Each tablet were weight 700 mg containing 250 mg theophylline (35.71%). The mass of tablet were prepared by mixing all of the compounds with mixing camber (Erweka AR 400). Then tablets were compressed by direct compression using a double punch tablet machine Erweka AR 400, Heusenstamm, Germany, with 13 mm flat round punches.

The physical properties of the tablets: The amount of the tablets from each formulation was picked randomly in order to evaluate the weight variation, the friability by using friabilator (Erweka TAR) and the hardness of the tablets by using hardness tester (Erweka TBH28). For measuring weight variation of the tablet, electronic balance (Ohaus TS120S) was used. The friability of the tablet was determined by Erweka-TAR.

Table 1: Composition (%) of theophylline matrix tablet models

	Formulation (% w/w)					
Ingredients	CPCS1	CPCS2	CPCS3	PCSN1	PCSN2	PCSN3
Theophylline	35.71	35.71	35.71	35.71	35.71	35.71
CPCS	30	40	50	-	-	-
PCSN	-	-	-	30	40	50
Stearic acid	1	1	1	-	-	-
Magnesium stearate	-	-	-	0.7	0.7	0.7
Talc	2	2	2	2	2	2
Lactose spray dried	31.29	21.29	21.29	31.29	21.29	11.29

***In vitro* drug release profiles of theophylline:** Drug release profiles were evaluated *in vitro* using a dissolution test apparatus (Electrolab TDT-08L, Korea). The paddle method was selected to perform the dissolution profiles of theophylline from hydrophilic polymer matrix. The same test for all of the formulations was carried out in 900 mL HCl solution (pH I.8) and phosphate buffer (pH 7.2), maintained at 37±0.5°C at a paddle rotation speed of 50 rpm. Withdrawing 5 mL filtered-samples up to 3 h monitored progress of the dissolution. The sample solutions were analyzed by Spectrophotometer (Shimadzu UV-1601) at 270.0 nm (pH 1.8) and at 271.4 nm (pH7.2). Cumulative percentage of drug release was calculated and the mean of three determinations was used in data analysis.

RESULTS AND DISCUSSION

Pregelatinized starch was phosphorilated by two different phosphoric reagents, $POCl_3$ and Na_2HPO_4 the reaction with $POCl_3$ yielded peregelatinized cassava starch di-ester phosphates or cross-linked bond, whereas Na_2HPO_4 produced peregelatinized cassava starch mono-ester phosphate. Overall, differentiation molecule structure of material is causation differential of the particle shape, as shown in Fig 1. Cassava starch posses the specific particle shape as shown in Fig 1A. Unlike the particle of pregelatinized starch that has changed to an amorphous and undefined shape (Fig 1B), the particle of cassava starch is semi crystal. Both CPCS and PCSN have similar particle forms as shown in Fig. 1C and D. Having more pores, the structure of the particle of pregelatinized phosphate cassava starch might be able to trap some water at room temperature that increase viscosity and gel strength. It was proven that both of pregelatized cassava starch phosphate esters possible to be used as hydrophilic polymer matrix for controlled

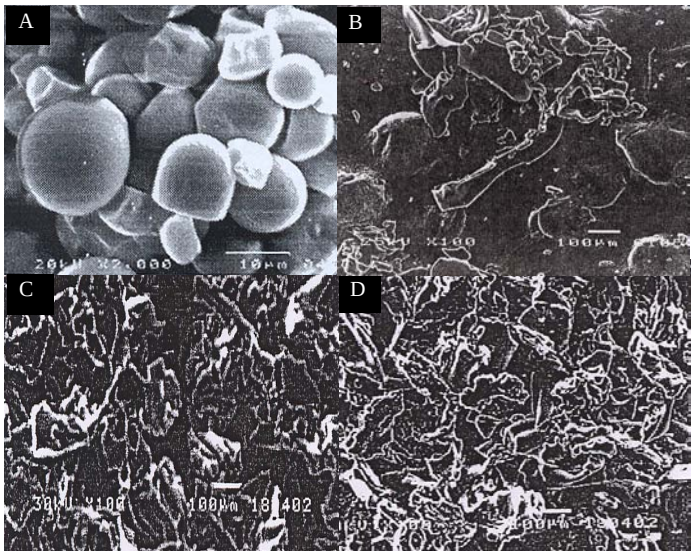

Fig. 1: Shape of (A) untreated natural cassava starch, (B) pregelatinized cassava starch, (C) CPCS, (D) PCSN

release tablet. On the other hand, cassava starch and starch phosphate esters are unable to swell in cold water at room temperature to increase viscosity and gel forming. This phenomenon made them being unable to be used as matrix controlled release tablet.

Table 2 shows the physico-chemical properties of CPCS and PCSN. They were used as monolithic matrix system of the tablet. Monolithic matrix concept is uniformly drug dispersed in polymer carrier like CPCS and PCSN, drug dissolve throughout a polymer matrix. To be monolithic matrix the material content in the formula higher than 30%, so it is perform the multiple functions of binder, filler and flow aid. It is versatile, being effective in variety of processing method for direct compression. Direct compression is the preferred method for preparation tablets, because low production cost and efficient in process. Direct-compression excipients become more valuable to formulator if they have multiple functionalities.

Viscosity: CPCS had the highest viscosity then in turn PCSN and pregelatinized cassava starch. The viscosity of CPCS value was 359.1 cps, whereas PCSN and pregelatinized cassava starch were 340.6 and 205.6 cps, respectively.

Gel forming: The gel strength of CPCS value was 27.00 g cm^{-1}, PCSN 24.80 g cm^{-1} and pregelatinized cassava starch 22.02 g cm^{-1}. The results showed that CPCS had the highest gel strength then PCSN and pregelatinized cassava starch. Both of viscosity and gel strength values showed that phosphorylation of pregelatinized cassava starch were able to alter the functional properties of the polymers.

Table 2: Physico-chemical properties of the pregelatinized starch phosphate

Parameters	CPCS	PCSN
Color	White to off white	
Form	Powder	
Los on drying (%)	6.12	5.80
Residue of ignition (%)	0.82	0.49
Density (bulk) g cm^{-3}	0.33	0.33
Density (tapped) g cm^{-3}	0.50	0.47
pH	5.85	5.56
Flow rate (g sec^{-1})	7.44	2.80
Angle of ripose (°)	40.16	38.80
Compressibility Index (%)	34.00	29.70

Table 3: Physical properties of theophylline tablet matrix

Formulation	Friability (%)	Hardness (kp)	Thickness (mm)	Diameter (mm)	Weight (mg)
CPCS1	0.38±0.52	5.80±0.78	3.97±0.04	13.1±0	709±3.70
CPCS2	0.49±0.68	6.96±1.30	4.05±0.11	13.1±0	709±3.73
CPCS3	0.69±0.97	6.50±0.89	4.19±0.05	13.1±0	709±2.50
PCSN1	0.33±0.46	9.33±0.56	3.97±0.03	13.1±0	718±3.00
PCSN2	0.38±0.52	9.90±1.08	4.85±0.02	13.1±0	728±2.12
PCSN3	0.59±0.83	9.04±1.74	4.29±0.02	13.1±0	737±3.05

The physical properties tablets: Diameter, friability, thickness, hardness and weight of the formulated tablets were described in Table 3. Having examined the tablets mass flow ability properties, in general, physical properties of the tablet are acceptable.

***In vitro* release profile of theophylline:** Figure 2, showed the release profiles of theophylline from three different concentrations of CPCS and PCSN (30, 40 and 50%) as

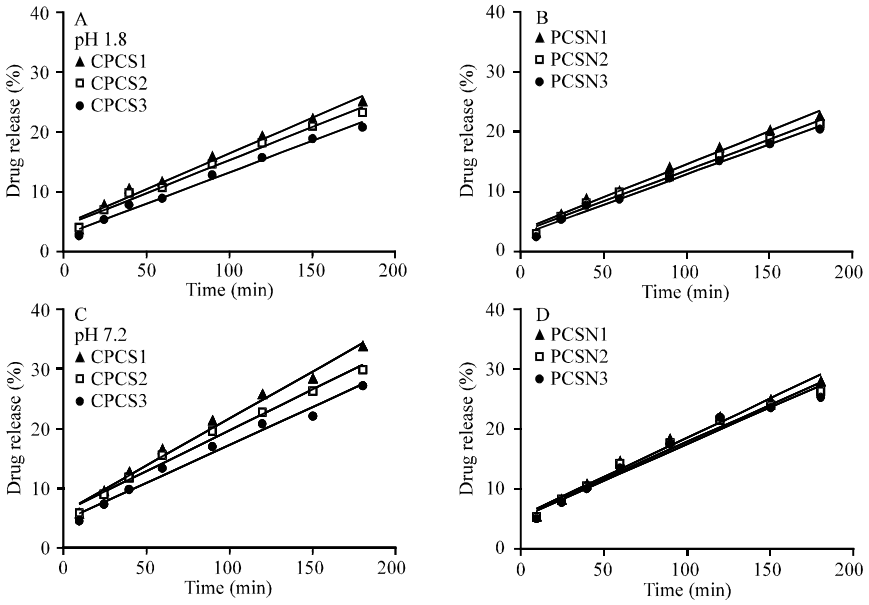

Fig. 2: Theophyline release from (A) CPCS matrices, (B) PCSN matrices (pH 1.8), (C) CPCS matrices, (D) PCSN matrices (pH 7.2)

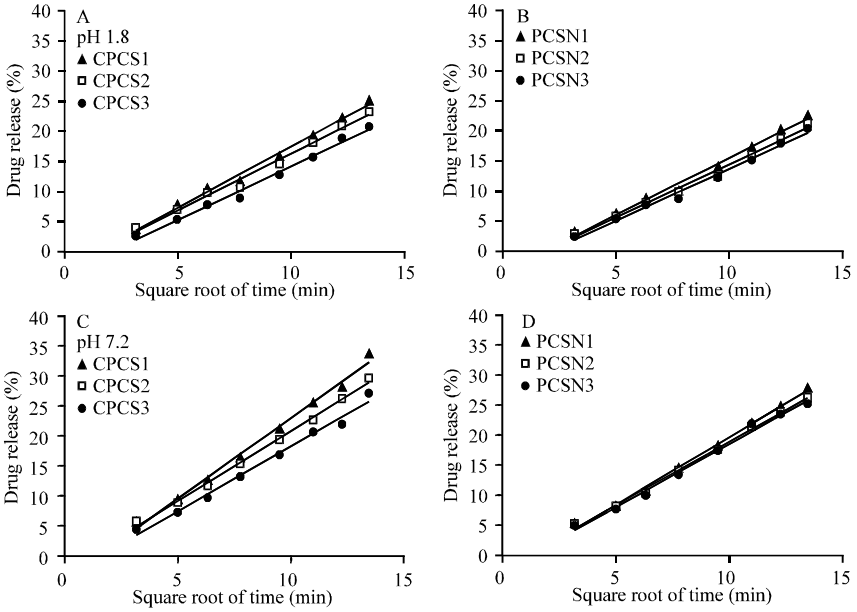

Fig. 3: Theophyline release based on square root of time from (A) CPCS matrices, (B) PCSN matrices (pH 1.8), © CPCS matrices, (D) PCSN matrices (pH 7.2)

polymer hydrophilic tablets matrix. The figure showed a linear correlation between the percentage of drug release and the time in both pH environments. In each time interval, the constant amount of drug has been released both of cross-linked pregelatinized cassava starch (CPCS) and mono-ester pregelatinized cassava starch phosphate (PCSN) into the solution. The figure showed zero-order kinetic dissolution in accordance to the equation of F(t) = kt. The figure indicated that in each time interval, the same amount of drug permeates to the solution. The drug release having the zero-order kinetic showed the constant amount of drug to be maintained on the blood level as indicated in a multiple dose regimen with an immediate-release drug product for period of times (Hennin *et al*., 2004). Both figures, showed that all the matrices containing CPCS and PCSN were able to

control up to 33% drug release in 3 h. Additionally, theophylline was released from the matrices between 20-50%, when $Q_{0,25}$ as the time equal to 0.25 D: 20-50% drug dissolved in the liquid. The therapeutics level might be maintained by the drug release for 12 h (Banacar, 1991). Consequently, the tablet could only be administered two times daily. The highest polymeric concentration of CPCS (50% w/w) indicated the slowest rate of drug release. The drug release from all tablets might be controlled by combination of diffusion and erosion delivery system. Overall, the pregelatinized cassava starch phosphate CPCS was more reasonable than PCSN for controlled release tablet dosages form as hydrophilic polymer excipient.

Figure 2 also showed that all release profiles were not affected by pH. It showed the same results to those of Geresh *et al*. (2004). This phenomenon indicated the gel form of the material being stable in acid and alkali medium. The gels build a natural barrier for drug to diffuse from the tablet. The drug release might also be controlled by erosion or combination of diffusion and erosion of the delivery system (Göpferich, 1996). The diffusion can be activated by external effect, such as swelling. It was also based on Fick's law describing the macroscopic transport of molecules (drug) by concentration gradient (Coviello *et al*., 1998). Derives starch is a biodegradable molecule. Matrices can naturally be eroded in the alimentary. Erosion characteristics were showed in Fig. 3, explaining the linear correlation of square root of time function ($F(t) = k\sqrt{t}$) (Lipidus and Lordi, 1968).

CONCLUSIONS

The regelatinized cassava starch phosphate CPCS was superior to PCSN for controlled release matrix in tablet, prepared by direct compression process. No significant difference of the drug release rate in pH 1.8 and pH 7.2, which represented the simulation condition of gastro intestinal liquid. The release of theophylline was influenced by the concentration of the hydrophilic matrix. The highest concentration (50%) of the matrix (CPCS) showed in the both pH the lowest drug release rate. The drug release tablet showed zero-order kinetic and may be controlled by combination of diffusion and erosion delivery system.

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