Journal of Medical Sciences

ISSN 1682-4474

science alert

ANSInet
an open access publisher
http://ansinet.com

Research Paper

J. Med. Sci., 9 (6): 249-256
15th August, 2009

Study of Mucoadhesive Microspheres Based on Pregelatinized Cassava Starch Succinate as a New Carrier for Drug Delivery

S. Surini, V. Anggriani and E. Anwar

The objective of this research is to study the application of Pregelatinized Cassava Starch Succinate (PCSS), a physically and chemically modified starch and the combinations with Carbopol 974P and hydroxypropylmethyl cellulose (HPMC) for preparing mucoadhesive microspheres by the spray-drying technique. The obtained-microspheres were characterized, including: morphology, particle size distribution, entrapment efficiency and mucoadhesive strength on the stomach and intestinal of rats. In addition, the *in vitro* drug release from the microspheres was performed in pH 1.2 and 7.2. The results showed that the produced microspheres of PCSS and its combination with HPMC and Carbopol 974P were irregular shape with a rough surface morphology and have particles sizes range of 2.5-28 μm. Propanolol hydrochloride (PH) was incorporated into the microspheres with an efficiency of range between 84-100%. On gastric mucosa, the microspheres of PCSS, HPMC and PCSS-HPMC were more mucoadhesive than the microspheres of Carbopol 974P and PCSS-Carbopol 974P. On the other hand, all kinds of the microspheres show good mucoadhesive properties on intestinal mucosa. Furthermore, the drug release from the microspheres produced pH-dependent extended-release in pH 1.2 HCl and pH 7.2 phosphate medium. During 8 h *in vitro* release study, the release of propanolol hydrochloride from the microspheres of PCSS-HPMC and PCSS-Carbopol 974P in pH 7.2 was slower than that in pH 1.2. The findings obtained revealed that PCSS microspheres have good mucoadhesive property on both of gastric and intestinal mucosa. Moreover, the addition of HPMC and Carbopol 974P to PCSS hydrophilic matrix significantly extended the drug release.

Key words: Microspheres, spray drying, mucoadhesive, pregelatinized cassava starch succinate, drug delivery

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

For further information about this article or if you need reprints, please contact:

S. Surini
Department of Pharmacy,
Faculty of Mathematic and
Natural Science,
University of Indonesia,
Depok, 16424, Indonesia

ANSInet
Asian Network for Scientific Information

Department of Pharmacy, Faculty of Mathematic and Natural Science,
University of Indonesia, Depok, 16424, Indonesia

INTRODUCTION

Mucoadhesive polymers are synthetic or natural macromoleculs which are capable of attaching to mucosal surfaces. The concept of mucoadhesive polymers has been introduced into the pharmaceutical literature more than 40 years ago and nowadays, it has been accepted as a promising strategy to prolong the residence time and to improve the specific localization of drug delivery systems on various membranes (El-Kamel *et al*., 2002; Yadav and Mote, 2008; Chowdary *et al*., 2003). So far, a considerable number of studies focusing on the mucoadhesive properties of a wide range of polymeric materials have been performed (El-Kamel *et al*., 2002; Shojaei and Berner, 2006). Diverse classes of polymers have been investigated for their potential use as bioadhesives. These include synthetic polymers such as polyacrilic acid and derivatives (El-Kamel *et al*., 2002) hydroxypropyl, methylcellulose and polymethacrylate derivatives, as well as naturally occurring polymers such as chitosan, hyaluronic acid, alginate, starch and derivatives (Shojaei and Berner, 2006). These materials are generally hydrophilic macromolecules that contain numerous hydrogen bond forming groups and will hydrate and swell when placed in contact with aqueous solution (Mortazavi, 2002).

Starch can be used as polymeric material. Starch is biocompatible, biodegradable and bioadhesive in nature (Yadav and Mote, 2008). The concept of using bioadhesive delivery system in the form of degradable starch microspheres for drug delivery was introduced (Illium, 2003). Starch is not only biodegradable, but also shows a high degree of swelling when in contact with aqueous medium. Starch forms a gel like system, with prolonged residence time in nose and significant contact with the nasal mucosa (Yadav and Mote, 2008; Illium, 2003). In addition, starch microspheres do not produce immune response (Yadav and Mote, 2008).

Cassava starch is an inexpensive and abundant polysaccharide, especially in Indonesia. It is found in nature as water insoluble semicrystalline granules which size varying from 5-35 μm (Breuninger *et al*., 2009). Although, starch is easily gelatinized or dissolved in water, it is still difficult to process due to the viscosity and thickening properties, which already occur at low solid contents. The range of functional properties of starch is restricted even for chemically modified starch with degree of substitution (Grabovac *et al*., 2005). Starch utilization as an excipient in pharmaceutical dosage form requires specific properties which are not had by native starch. Numerous physical and chemical modifications may be applied at starch to impart properties that are useful for particular application. One of physical and chemical modification is esterification of pregelatinized starch by using succinic anhydride, which is occurred the interaction between succinate groups with hydroxyl group of amylopectin and amylase chains (Chiu and Solarek, 2009).

In this study, Pregelatinized Cassava Starch Succinate (PCSS), a physically and chemically modified starch, has been produced and characterized. The PCSS is biocompatible and biodegradable polymer, since, it is one of starch derivatives in nature. Pregelatinized starch was produced by mechanical processing to rupture all parts of the granules in the presence of water and subsequently dried (Langan, 1986). The major compound in starch granules are amylase and amylopectin that leach out from the granules when the granules ruptured. Obtained pregelatinized starch was esterified with succinate anhydride in base medium. Functional properties of chemical starch modification depend on degree of substitution (DS). In the present study, DS of the PCSS is 0.1% as product of esterification of hydrolized starch. The properties of high DS starch ester depend on the starting material, the length of the alkyl chain in the substituent and the method of the preparation. Hydroxylpropyl group are hydrophylic in nature, therefore, the PCSS can improve cold water swelling and gel strength. Both of the properties is useful as excipient in pharmaceutical dosage forms.

The aim of this work was the possible application of PCSS for the preparation of mucoadhesive microspheres, since, PCSS is a promising of natural polymer material for mucoadhesive. The PCSS microspheres were prepared by spray drying technique; a one step process that offers the advantages of good production yield and reproducibility. The microspheres were characterized in terms of particle size and morphology, percentage yield, entrapment efficiency, moisture content, mucoadhesive property (mucoadhesive strength) and *in vitro* drug release. The PCSS was also combined with HPMC or Carbopol 974P as hydrophilic polymers that sustaining and controlling drug release from microspheres. Moreover, the effect of HPMC and Carbopol 974P on mucoadhesive property and *in vitro* drug release of PCSS microspheres was studied. Microspheres HPMC and Carbopol 974P alone were used as comparisons; Propanolol hydrochloride has been chosen as a model drug.

MATERIALS AND METHODS

Study conduct: The study was carried out from May 2008 to May 2009 in Department of Pharmacy, Faculty of Mathematic and Natural Science, University of Indonesia, Depok, Indonesia.

Materials: Cassava starch (Sungai Budi Industry, Indonesia), propranolol hydrochloride (Societa Italiana, Italy), Carbopol 974P (Noveon, Swiss), Hypromellose® (hydroxypropylmethyl cellulose) grade 60 SH-50 (ShinEtsu, Japan), Cellophane (Union Carbide Corporation, Chicago), simulated gastric (pH 1.2) and simulated intestinal (pH 7.2) medium solutions were prepared according to the relevant USP monograph.

Methods

Preparation of pregelatinized cassava starch: Suspension of cassava in water (1:3) was cooked until form clarity pasta and then dried using double drum dryer at 80°C. The dried product was pulverized and sieved with mesh 100.

Esterification of pregelatinized starch with succinic acid: Pregelatinized Cassava Starch (PCS) was esterified according to the modification method that described by Jawarenko (1986). The PCS was esterified with succinate anhydride 4% (based on dried weight of PCS) under base condition. After the esterification process finished, the esterified PCS suspension was dried using double drum dryer.

Preparation of mucoadhesive microspheres: Mucoadhesive microspheres were prepared by spray drying technique. Aqueous solution containing different combination and concentration of polymer (Table 1) were prepared by dissolving PCSS, HPMC or Carbopol 934P in distilled water under stirring at room temperature and then the model drug, Propanolol Hydrochloride (PH) was added to the polymer solution. The microspheres were obtained by spraying the solutions through the nozzle (0.7 mm of diameter) of a spray dryer model Mini Spray Dryer Büchi B-290 (Büchi Labortechnik AG, Flawil, Switzerland). The condition of the spray-drying process were: inlet air temperature 195°C, outlet air temperature 95°C, pump setting 40 mL min^{-1} and the nozzle air pressure 4 bars. Microspheres were then collected into the final bottom vessel of the spray dryer.

Morphological and shape examination: Scanning electron microscope (LEO 420i, England) was used to examine the shape and surface morphology of mucoadhesive microspheres. Samples of microspheres were dusted onto double side tape on an aluminum stub. The stubs were then coated with a layer of gold under vacuum. The samples were imaged using a 12 kV electron beam.

Table 1: Formulation of microspheres

	Microspheres formulations						
Material (g)	PCSS	PCSS/ HPMC 1	PCSS/ HPMC 2	HPMC	PCSS/ Cp 1	PCSS/ Cp 2	Cp
Propanolol HCl	0.4	0.4	0.4	0.4	0.4	0.4	0.4
PCSS	4	4	4	-	4	4	4
HPMC	-	0.5	1	1	-	-	-
Carbopol 974P	-	-	-	-	0.5	0.8	0.8
Aquadest (mL)	100	100	100	100	100	100	100

Particle size measurements: The prepared microspheres were sized by using particle size analyzer Coulter LS_100 (Beckman Coulter, USA). The size of the microspheres was determined in suitable medium, a non-dissolving dispersion medium. The particle size of the microspheres was expressed as the volume surface diameter, d_{vs} (μm).

The yields of production: The production yield (percent w/w) was calculated from the ratio of weight of a dried microspheres recovered from each formula to the weight of initial dry weight of starting materials.

Entrapment efficiency: Samples of the microspheres containing 5 mg propranolol HCl were crushed and dissolved in distilled water with support by ultrasonic stirrer for about 3 h. The solution was filtered and the filtrate was assayed by UV-VIS spectrophotometer V-530 (Jasco, Japan) at wavelength 289 nm. The entrapment efficiency was calculated from the ratio of actual drug content to theoretical drug content.

Mucoadhesive property: The forced required to separating microsphere from freshly excised rat stomach and rat intestine was measured in simulated gastric solution of pH 1.2 and simulated intestinal solution of pH 7.2 using a modified method on a TA.XT2 Texture Analyzer 3305 (Rheoner, Germany) connected to a personal computer and running with a XTRA Dimension software package. A section of tissue was cut from a healthy rat stomach and rat intestine and then washed carefully by isotonic saline solution to remove its contents. The 4 mg of microspheres were spread into a uniform monolayer over the tissue. The prepared tissue was equilibrated for 20 min before and maintained during the test in pH 1.2 HCl and pH 7.2 phosphate medium at 37°C. Furthermore, the section of the tissue was placed, mucosal side out, over the instrument probe and secured with an aluminum cap with a hole of 10 mm diameter in its center. The hydrated microspheres were brought into contact with the tissue with a 2 g force and maintained for 1 min. At the end of this time, the probe was withdrawn at a rate of 0.1 mm sec^{-1} and the force/time curve was recorded until the polymer became detached from the mucus layer. The maximum force required for detachment was determined directly from the recorded curve.

***In vitro* release studies:** *In vitro* drug release test was performed with a modified diffusion apparatus. In order to localizing the microspheres, cellophane was used as diffusion membrane (diameter was about 3 cm). Samples of microspheres containing 4 mg propranolol HC1 were added on the cellophane and tested in 100 mL of HC1 medium (pH 1.2) and phosphate medium (pH 7.2). The rotational speed was set at 100 rpm and the temperature for the diffusion medium was maintained at 37±0.5°C. Samples (10 mL) were withdrawn periodically at time points (0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7 and 8 h) and for each withdrawal the corresponding volume was replaced with fresh medium at the same temperature. The samples were then analyzed by UV-VIS spectrophotometer (V-530, Jasco, Japan) at wavelength 289 nm.

RESULTS

The obtained PCS was white-light powder and have rendement 91% from dry weights of cassava starch. Esterified PCS with succinate anhydride produced PCSS, which was light brown powder and have degree of subtitution (DS) 0.1. Spray drying was rapid and simply involved the preparation of a feed-solution containing drug and polymer. All the microspheres were produced by the spray-drying method with yields of production of 28 to 56% (Table 2). The microspheres entrapment efficiency of the model drug, PH, was in the range of 77 to 100% (Table 2). Combination PCSS with HPMC or Carbopol 974P in microspheres formulation increased the entrapment efficiency. The SEM micrographs of the micropheres showed that PCSS microspheres and all microspheres consisted of PCSS produced irregular shape with a rough surface morphology (Fig. 1a-c). Particle size of the microspheres was measured using Coulter laser diffraction method and the results are expressed as $d_{,,}$. Particle size analyses indicate that microspheres have $d_{,,}$ values of about 5-35 μm and median values 2-28 μm (Table 2).

The strength values of mucoadhesion and the mean maximum forces required to breaking the adhesive bond between the microspheres and the rat gastric or intestine mucosa in the presence of different medium is shown in

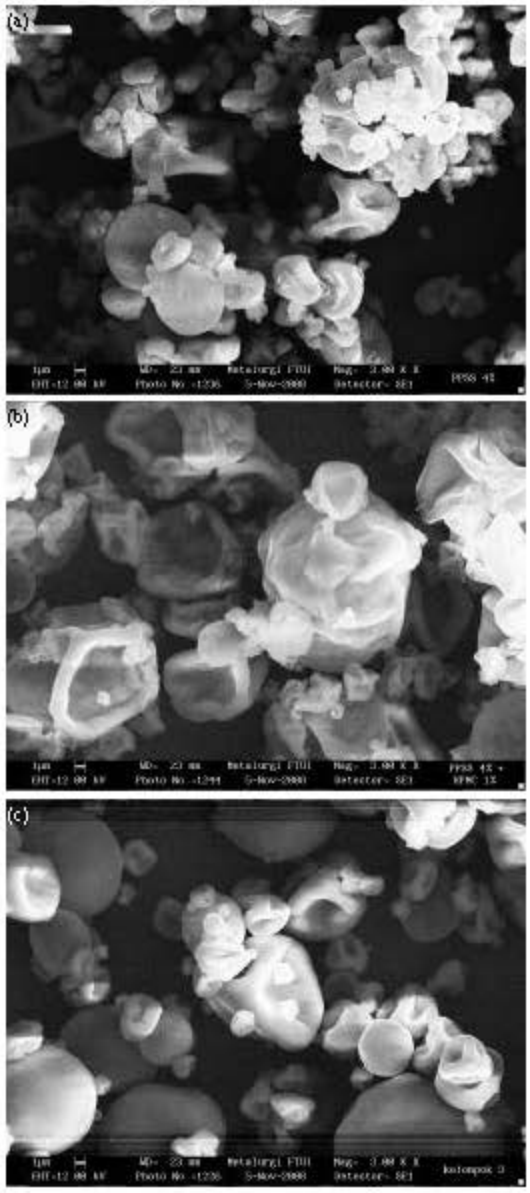

Fig. 1: Scanning electron micrograph of microspheres of: (a) PCSS, (b) PCSS/HPMC 2 and (c) PCSS/Carbopol 2. Scale bar 1 μm and magnification was 3000x

Table 2: Yield, entrapment efficiency, moisture content and particle size of microspheres

Microspheres	Percentage yield (w/w)	Entrapment efficiency (%)	Moisture content (%)	Mean size diameter (m)	Median particle size diameter (m)
PCSS	28.09	83.73	6.32	5.30	2.52
PCSS/HPMC 1	47.02	98.28	5.08	4.20	2.59
PCSS/HPMC 2	45.59	100.38	5.32	4.13	2.55
HPMC	55.71	87.06	6.68	2.70	2.65
PCSS/Cp 1	35.65	84.59	4.43	15.70	25.19
PCSS/Cp 2	37.85	90.14	5.43	35.81	28.08
Cp	52.75	76.73	5.14	8.15	1.92

Table 3: The adhesion strength of the prepared microspheres

	Adhesive strength (gF)	
Microspheres	Stomach	Intestine
PCSS	4.87±0.15	4.17±0.22
PCSS/HPMC 1	4.10±0.10	4.50±0.00
PCSS/HPMC 2	4.47±0.15	4.27±0.12
HPMC	4.67±0.06	5.27±0.25
PCSS/Cp 1	3.50±0.00	4.43±0.12
PCSS/Cp 2	3.23±0.21	5.27±0.21
Cp	3.60±0.52	4.93±0.06

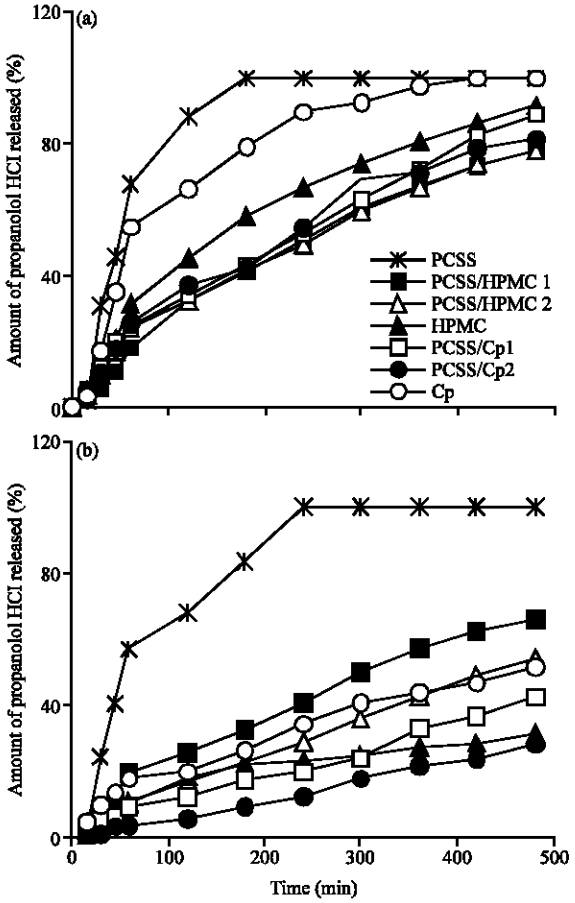

Fig. 2: Propanolol HCl release from microspheres in (a) the medium of hidrochloride pH 1.2 and (b) phosphate buffer pH 7.2, at 37°C. Each point represent the Mean±SD of three determinations

Table 3. The results showed that the microspheres had good mucoadhesive properties and could adequately adhere on stomach and intestine mucosa. One way ANOVA indicated that the effects on adhesion of polymers and medium were all significant ($p<0.05$). The microspheres of PCSS showed better adhesion at gastric (medium of pH 1.2) than that intestine mucosa (medium of pH 7.2). Microspheres consisted of HPMC, showed relatively high mucoadhesive strength in rat gastric and intestine mucosa with insignificantly values ($p<0.05$).

In vitro release profile of propanolol microspheres formulations are shown in Fig. 2a and b. The propanolol release from the microspheres based on PCSS, HPMC and Carbopol 974P formulations show different percentage of the drug release during 8 h of *in vitro* release study. Drug release from microspheres of PCSS showed the highest values and was found to be insignificantly different in both medium ($p>0.05$). The addition of HPMC or Carbopol 974P in PCSS matrices were reduced the release of propanolol from the microspheres. Beside that, the propanolol release was influenced by dissolution medium. The results show the propanolol release in medium of pH 1.2 is higher than in medium of pH 7.2.

DISCUSSION

Mucoadhesive microspheres based on modified starch were investigated in order to prolong contact time at the optimal site of absorption, thus, enhance drug absorption and increase drug bioavaibility. In this study, production yield of the microspheres shows relatively low values (28-56%). It can be explained by the structure of the spray dry apparatus, which is not equipped with a trap to recover the smaller and lighter particles which are exhausted by the aspirator (Gavini *et al*., 2006). The microspheres prepared using PCSS showed the lowest values, because during the process of drying, its solution adhered to the surface of chamber of the spray dryer and the nozzle of spray dryer was plugged up due to the starch granules in the solution (Bayram *et al*., 2004). It is well explained that above a certain temperature (glass transition temperature), materials containing sugars (i.e., starch) undergo structural changes towards a more sticky (rubbery) state. The transition may be important both for cohesion of particles to one another in agglomeration and adhesion of particles to walls (Langrish and Fletcher, 2001).

Propanolol HCl, as a model drug, was entrapped in the microspheres as amount of 77-100% (Table 2). The results revealed that the addition HPMC or Carbopol 974P into PCSS microspheres formulation might increase the entrapment efficiency. The results agreed with Gharsallaoui *et al*. (2007), they revealed that the efficiency can be increased by increasing wall solution solids concentration which can be related to the effect of wall solids concentration on the formation of surface core prior to the formation of crust around the drying droplets.

The SEM micrographs of the microphores based on PCSS produced irregular shape with a rough surface morphology (Fig. 1). However, Carbopol 974P microspheres previously prepared by spray-drying method showed smooth spherical morphology, while HPMC showed crumpled surface and coalesced with each

other (Harikarnpakdee *et al*., 2006). The irregular shape of microspheres consisted of HPMC or PCSS were attributed to reduction in external volume as a result of drying process. Rapid loss of water and heating promotes stresses in the cellular structure of the materials, leading to a change in shape by means of shrinkage and formation of concave surface (Al-Muhtaseb *et al*., 2004). Moreover, materials containing high molecular weight of sugars have less capacity to act as plasticizers which is important for the formation of spherical microcapsules with smooth surface (Loksuwan, 2006). However, the rough texture of microspheres surface brings an advantage to the adhesion through stronger mechanical interactions (Vasir *et al*., 2003).

The particle size of the obtained microspheres has d_{vs} and median values of 5–35 and 2-28 μm, respectively. The particle size might be influenced by amount of polymer concentration in microspheres formulas. It was observed that as the amount of polymer concentration increased in microspheres, the particle size also increased proportionally. The reason for which may be due to the increase in viscosity of droplets during atomization process of drying (Yadav and Mote, 2008). Meanwhile, the low polymer concentration was not able to give the higher particle size as the droplet size was small and most of the part of drop consisted of solvent (less viscous) which would evaporate leaving the small particles (Rathananand *et al*., 2007). Moreover, when the less viscous droplet was dried, the water loss phenomenon causes shrinkage to be occurred and allowed to reduction the diameter size of microspheres. Whereas more viscous solution could hindered the materials its self from undergo the shrinkage process. For that reason, increasing in polymers is contributed to an increase in diameter size of microspheres.

Mucoadhesion properties of the produced microspheres to stomach and intestine of rat were studied using Texture analyzer. Mucoadhesion strength is the mean maximum forces required to breaking the adhesive bond between the microspheres and the rat gastric or intestine mucosa in the presence of different medium. The results showed that the microspheres have good mucoadhesive properties and could adequately adhere on stomach and intestine mucosa. The microspheres of PCSS showed better adhesion at medium of pH 1.2 than that of pH 7.2, since, hydroxyl groups and ester of PCSS might be in protonated form with small degree in ionization. Adhesion may occur through hydrogen bonding of the unionized forms (Tur and Hung-Seng, 1998). Increase in pH of medium produces suitable degree of ionization and may causes excessive microspheres hydration. This occurrence could affect to a reduction in the strength of polymer-mucosa bound due to the formation of slippery mucilage. There is a double effect of the water excess in mucoadhesive properties. Firstly, the gel consistency is reduced; secondly, water competes against functional groups of sugars (oligosaccharides from mucus) present in mucosa surface for the formation of hydrogen bonds with the hydroxyl groups of the polymers (Accili *et al*., 2004). As a consequence, PCSS has a stronger adhesion property in presence of a low amount of ionized forms.

Microspheres consisted of Carbopol 974P showed the higher value adhesion in rat intestine than that gastric mucosa. At higher pH levels, repulsion of carboxyl groups from Carbopol 974P changes the spatial conformation from a coiled state into a rod like structure making them more readily available for inter-diffusion and interpenetration with the mucin chains (Andrews *et al*., 2008). Microspheres consisted of HPMC showed relatively high mucoadhesive strength in both of rat gastric and intestine mucosa. Since, HPMC is non-ionic polymer, the change of pH seems would not influence the mucoadhesive properties. As can be seen in Table 3, combination between two polymers, mainly showed reduction in mucoadhesive properties due to possible formation of hydrogen bonds between the hydroxyl groups of PCSS and the functions groups of HPMC or Carbopol 974P (Gharsallaoui *et al*., 2007). This phenomenon could hinder the formation of strong mucoadhesive bond between interacting polymers and both mucosa surfaces and as a result of reducing its mucoadhesive strength. However, the mucoadhesion property of Carbopol 974P from microspheres in formula PPCS/Cp 2 were less influenced by the presence of PCSS and revealed the higher mucoadhesion values than its individual polymers in intestine mucosa.

In vitro release study of the propanolol microspheres was performed in medium pH 1.2 and 7.2. The combination of polymers in microspheres formulae affects the drug release from the microspheres. The propanolol release from PCSS microspheres showed the highest value compared to that from the microspheres consists of the combination PCSS and HPMC or Carbopol 974P. Since, PCSS could swells progressively and the gel layer at the surface of PCSS microspheres erodes quickly, it was resulting in a fast drug release from PCSS microspheres. The addition of HPMC or Carbopol 974P in PCSS matrices were reduced the propanolol release from the microspheres. This result shows that as the polymer amount increases, the drug releases slower because of the longer diffusion path in microspheres with the higher amount of polymers.

The propanolol release from microspheres consisted of Carbopol 974P showed the lowest values in pH 7.2

Table 4: Release kinetic based on Peppas equation

	Peppas equation (n value)	
Microspheres	pH 1.2	pH 7.2
PCSS	0.83	0.81
PCSS/HPMC 1	0.78	0.78
PCSS/HPMC 2	0.73	0.73
HPMC	0.78	0.75
PCSS/Cp 1	0.73	0.63
PCSS/Cp 2	0.75	0.65
Cp	0.80	0.63

medium. This was due to its good swelling property in medium of pH above pKa of Carbopol (6±0.5). In addition, Carbopol 974P is an anionic polymer which could undergo complexation with weak basic drugs such as propanolol. In most cases, the drug-carbopol complex has less solubility than the pure drug. This property will support the sustained release properties from matrix containing carbopol (Mariageraldrajan, 2007).

As shown in Fig. 2, the propanolol release in medium of pH 1.2 is higher than in medium of pH 7.2. It may due to the higher solubility of propanolol in acidic medium, since, propanolol has the characteristics of weakly basic drugs. Therefore, it shows that propanolol HCl has a pH-dependent solubility. In earlier study, the solubility in pH 1.2 was found to be 225 and 130 mg mL^{-1} at medium phosphate of pH 6.8 (Takka *et al*., 2001).

Peppas model could explain the release mechanisms involved in the drug release. The release exponent n in Peppas equation (Eq. 1) based on the geometry device, can be used to identify the release mechanism (Siepmann and Peppas, 2000):

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where, M_t/M_∞ is the fraction of drug release at time t, k is the kinetic constant and n is the release exponent. Peppas equation can explain drug delivery with three different geometries i.e, slab, sphere and cylinder (Harikarnpakdee *et al*., 2006). Matrices from microspheres can be considers as spheres. In systems with spheres geometry, n = 0.43 indicates fickian diffusion, $0.43<n<0.85$ indicates non-fickian (anomalous) transport, n =0.85 indicates case II transport (zero order drug release/time independent), $n>0.85$ indicates super case II transport (Loksuwan, 2006). As are shown in Table 4, values of n exponent release of pH from mucoadhesive microsphere lies in range between $0.43<n<0.85$. This is indicating that the releases from microspheres are based on non-fickian (anomalous) transport and the releases are controlled by diffusion and erosion mechanism (Harikarnpakdee *et al*., 2006).

The finding results concluded that microspheres consisted of PCSS have good mucoadhesive property on both of gastric and intestinal mucosa. Moreover, the addition of HPMC and Carbopol 974P to PCSS hydrophilic matrix significantly extended the drug release. PCSS microspheres thus, present its great potential as a mucoadhesive microspheres as well as a hydrophilic matrix for controlled drug delivery.

ACKNOWLEDGMENT

Authors are thankful to University of Indonesia and Education Ministry of Indonesia for financial support.

REFERENCES

Accili, D., G. Menghi, G. Bonacucina, P. Di Martino and G.F. Palmieri, 2004. Mucoadhesion dependence of pharmaceutical polymers on mucosa characteristics. Eur. J. Pharm. Sci., 22: 225-234.

Al-Muhtaseb, A.H., W.A.M. McMinn and T.R.A. Magee, 2004. Shrinkage, density and porosity variations during the convective drying potato starch gel. Proceedings of the 14th International Drying Symposium C, Aug. 22-25, Sao Paulo, Brazil, pp: 1604-1611.

Andrews, G.P., T.P. Laverty and D.S. Jones, 2008. Mucoadhesive polymeric platforms for controlled drug delivery. Eur. J. Pharm. Biopharm., 71: 505-518.

Bayram, O.Z., M. Bayram and A.R. Tekin, 2004. Spray drying of sumac flavour using sodium chloride, sucrose, glucose and starch as carriers. J. Food Eng., 69: 253-260.

Breuninger, W.F., K. Piyachomkwan and K. Sriroth, 2009. Tapioca/Cassava Starch: Production and Use. In: Starch: Chemistry and Technology, BeMiller, J. and R. Whistler (Eds.). 3rd Edn., Elsevier, New York, pp: 541-568.

Chiu, C. and D. Solarek, 2009. Modification of Starches. In: Starch: Chemistry and Technology, BeMiller, J. and R. Whistler (Eds.). 3rd Edn., Elsevier, New York, ISBN: 978-0-12-746275-2, pp: 629-655.

Chowdary, K.P.R., B. Suresh, B. Sanggeta and K. Reddy, 2003. Design and evaluation of diltiazem mucoadhesive tablet for oral controlled release. Saudi Pharm. J., 11: 201-205.

El-Kamel, A., M. Sokar, V. Naggar and S. Al-Gamal, 2002. Chitosan and sodium alginate-based bioadhesive vaginal tablets. AAPS Pharm. Sci., 4: E44-E44.

Gavini, E., A.B. Hegge, G. Rassu, V. Sanna and C. Testa *et al*., 2006. Nasal administration of carbamazepine using chitosan microspheres: *In vitro*/*in vivo* studies. Int. J. Pharm., 307: 9-15.

Gharsallaoui, A., G. Roudaut, O. Chambin, A. Voilley and R. Saurel, 2007. Aplications of spray-drying in microencapsulation of food ingredients: An overview. Food Res. Int., 40: 1107-1121.

Grabovac, V., D. Guggi and A. Bernkop-Schnurch, 2005. Comparison of the mucoadhesive properties of various polymers. Adv. Drug Delivery Rev., 57: 1713-1723.

Harikarnpakdee, S., L. Vimolmas, N. Sutanthavibul, N. Garnpimol and C. Rittidej, 2006. Spray-dried mucoadhesive microspheres: Preparation and transport through nasal cell monolayer. AAPS Pharm. Sci. Tech., 7: E79-E88.

Illium, L.J., 2003. Nasal drug delivery-possibilities, problems and solution. J. Control. Release, 87: 187-198.

Jawarenko, W., 1986. Acetilated Starch and Miscellaneous Organic Esters. In: Modified Starches: Properties and Uses, Wurzbug, O.B. (Ed.). CRC Press, Florida, ISBN: 0-8493-5964-3, pp: 55-77.

Langan, R.E., 1986. Food Industry. In: Modified Starches: Properties and Uses, Wurzbug, O.B. (Ed.). CRC Press, Florida, ISBN: 0-8493-5964-3, pp: 199-212.

Langrish, T.A.G. and D.F. Fletcher, 2001. Spray drying of food ingredients and applications of CFD in spray drying. Chem. Eng. Process., 40: 345-354.

Loksuwan, J., 2006. Characteristic of microencapsulated β-carotene formed by spray drying with modified tapioca starch, native tapioca starch and maltodextrin. Food Hydrocoll., 21: 928-935.

Mariageraldrajan, N., 2007. Novel carbopol-wax blends for controlled release oral dosage forms. A Dissertation the University of Tennessee Health Science Centre, pp: 14-30. http://etd.utmem.edu/WORLD-ACCESS/rajan/2007-011-Rajan.pdf

Mortazavi, S.A., 2002. A comparative study between the strength and duration of mucosa-adhesion of transbuccal carbomer based aqueous gels. Iran. J. Pharm. Res., 1: 7-13.

Rathananand, M., M. Kumar, A. Shirwaikar, R. Kumar, D.S. Kumar and R.S. Prasad, 2007. Preparation of mucoadhesive microspheres for nasal delivery by spray drying. Indian J. Pharm. Sci., 69: 651-657.

Shojaei, A.H. and B. Berner 2006. Gastric Retentive Dosage Form. In: Design of Controlled Release Drug Delivery System, Li, X. and B.R. Jasti (Eds.). McGraw-Hill, New York, pp: 173-195.

Siepmann, J. and N.A. Peppas, 2000. Modelling of drug release from delivery system based on hydroxypropylmethylcellulose (HPMC). Adv. Drug Deliv. Rev., 48: 139-157.

Takka, S., S. Rajbhandari and A. Sakr, 2001. Effect of anionic polymers on the release of propanolol hydrochloride from matrix tablets. Eur. J. Pharm. Biopharm., 52: 75-82.

Tur, K.M. and C. Hung-Seng, 1998. Evaluation of possible mechanism(s) of bioadhesion. Int. J. Pharm., 160: 61-74.

Vasir, J., K.K. Tambwekar and S. Garg, 2003. Bioadhesive microspheres as a controlled drug delivery system. Int. J. Pharm., 255: 13-32.

Yadav, A.V. and H.H. Mote, 2008. Development biodegradable starch microspheres for intranasal delivery. Indian J. Pharm. Sci., 70: 170-174.