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RESEARCH PAPER

Hydroxypropyl Starch Nanoparticles as Controlled Release Nanocarriers for Piperine

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ABSTRACT

Hydroxypropyl starch was synthesized by modified sago starch with hydroxypropylation reaction. Hydroxypropyl starch nanoparticles with mean particle sizes of 110 nm are obtained by controlled precipitation through the drop-wise addition of dissolved hydroxypropyl starch solution into excess absolute ethanol. Piperine was loaded onto hydroxypropyl starch nanoparticles and native starch nanoparticles via the in-situ nanoprecipitation process. Hydroxypropyl starch nanoparticles exhibited higher piperine loading capacity as compared to native starch nanoparticles with the maximum loading capacity of 0.46 and 0.33 $mg.mg^{-1}$, respectively. Piperine was release from hydroxypropyl starch nanoparticles in a slow and sustained manner at pH 1.2 over the period of 24 hours. Whereas piperine was completely released from native starch nanoparticles within 16 hours.

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INTRODUCTION

Piperine is a naturally occurring alkaloid and it is the major bioactive component of pepper, which gives pungency and biting taste to it. Several studies have demonstrated that piperine possesses various beneficial health and therapeutic properties and most recently, piperine also showed chemopreventive and antioxidant activities [1]. Besides, it also has anticarcinogenic, stimulatory, anti-inflammatory, antimicrobial and antiulcer activities [1, 2]. However, the pharmaceutical activities of piperine are limited due to its low water solubility and its toxic effect on the central nervous and reproductive system when being used in high concentrations [1, 3]. These limitations have prompted many researchers to attempt to encapsulate piperine onto various nanoparticles in order to enhance its water solubility, bioavailability, and efficacy. There are several studies in which piperine was loaded onto nanoparticles. For example, piperine and curcumin were loaded onto zein-chitosan nanoparticles and 89% piperine encapsulation efficiency was achieved [2]. Piperine also showed high encapsulation efficiency (90.5%) when being encapsulated onto nanosize liposomes [4].

Studies have shown that starch nanoparticles are promising nanocarriers for various drugs and nutraceutical products due to its advantages, such as improving drug solubility and stability, decreasing drug toxicity and high drug loading capacity. In view of this, some researchers have attempted to load curcumin onto starch nanoparticles via the in-situ nanoprecipitation method. The maximum loading efficiency of 78% was achieved and the curcumin was released in a sustained way within 10 days from the nanoparticles with mean particle sizes of 87

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nm [5]. A model drug 5-aminosalicylic acid was also loaded onto crosslinked starch nanoparticles which are 40 nm in size and the maximum drug loading capacity achieved was 0.302 $g.g^{-1}$ [6].

However, starch is naturally unsuitable for most of the technological and biomedical applications in its native state due to its high retrogradation and syneresis besides having poor processability and low water solubility. Therefore, many types of modifications including blending and chemical modifications such as hydroxypropylation, oxidation and crosslinking were carried out to overcome the abovementioned limitations and improve its properties. Starch molecules possess large numbers of hydroxyl groups which could serve as the active sites for modification *via* various chemical reactions. Chemical modification is the most efficient approach to customize the overall properties and performance of native starch [7].

Hydroxypropyl starch can be prepared by the etherification reaction of native starch with propylene oxide in the presence of a strong alkaline catalyst. The hydroxyl groups are substituted with hydroxypropyl groups through the nucleophilic substitution reaction mechanism. Studies showed that hydroxypropylation reduced the retrogradation property of starch to recrystallize and it is more stable at high temperatures. The hydroxypropyl group has also been proven to have positive swelling effect on polymers in matrices with neutral pH, therefore providing a controlled and sustained drug release profile [8, 9].

There have been studies that have reported the synthesis of modified starch nanostructures (Table 1), however, up to our knowledge, this is the first time hydroxypropyl starch nanoparticles were prepared and loaded with piperine [10]. In this work, we report the synthesis of hydroxypropyl starch by chemical modifications of the native sago starch using hydroxypropylation methods. Subsequently, piperine loaded hydroxypropyl starch nanoparticles were prepared by *in-situ* nanoprecipitation method. Formulation parameters that affected the loading capacity and release profiles of piperine were investigated in order to determine the optimum conditions for controlled release of piperine.

MATERIALS AND METHODS

Materials

Native sago starch powder was obtained from a local grocery store. Hydrochloric acid (HCl), sulphuric acid (H_2SO_4), sodium hydroxide (NaOH) and potassium hydroxide (KOH) were purchased from Merck. Propylene oxide was procured from Acros Organic (USA). Sodium thiosulfate was purchased from R&M Chemicals, Essex, UK. Piperine was acquired from Sigma Aldrich. Absolute ethanol was obtained from HmbG Chemicals (Hamburg, Germany). All chemicals were used without further purification. Ultrapure water (~18.2 MΩ•cm, 25°C) was obtained from the Water Purifying System (ELGA, Ultra Genetic).

Synthesis of hydroxypropyl sago starch nanoparticles

Hydroxypropylation of sago starch was performed according to the reported method with slight modifications [6, 13]. Anhydrous sodium sulfate (Na_2SO_4) (20%, w/v) was added to the

Table 1. Summary of synthesis of modified starch nanostructures.

Starch source	Modification	Yield	Application	Reference
Corn starch	Acetylation	Nanoparticles	Drug delivery	[10]
Maize starch	Crosslinking and esterification	Nanocrystals		[11]
Corn starch	Oxidation	Nanofibers		[12]
Soluble starch	Crosslinking	Nanoparticles	Drug delivery	[6]

starch slurry (20%, w/v). The starch slurry was stirred for 30 minutes and the pH was adjusted to 10.5 with the addition of NaOH (5%, w/v). Then, propylene oxide (5%, 10%, 15%, and 20%) was added as an etherifying agent. The resulting suspension was mixed thoroughly and the reaction was maintained at 40 °C for 24 hours. The reaction was then terminated by adjusting the pH to 5.5 using HCl (10%, v/v). The resulting hydroxypropyl starch solution was added drop-wise into absolute ethanol in the ratio of 1:20 under constant stirring (900 rpm). Hydroxypropyl starch nanoparticles were precipitated and were centrifuged, washed with absolute ethanol and dried at 60 °C for 24 hours [14].

Molar Substitution (MS)

The hydroxypropyl group in the modified starch was determined according to the reported method [15, 1]. A sample of hydroxypropyl starch (0.05 g) was weighed into a 100 mL volumetric flask and 25 mL of sulphuric acid (H_2SO_4) (0.5 M) was added. A sample of native starch was prepared in the same manner. The flasks were placed and heated in boiling water until the solution became clear. The samples were allowed to cool before the contents were diluted to 100 mL with UPW. The tubes were immersed in an ice bath before 8 mL of concentrated H_2SO_4 solution were added dropwise into each tube. The solution was mixed well and the tubes were placed in a boiling water bath for 3 minutes. The tubes were then transferred to an ice bath until the solution was chilled. Approximately 0.6 mL of ninhydrin reagent ($C_9H_6O_4$) was added, and the tubes were immediately shaken well and leave at room temperature for 100 minutes. The volume of the solution in each tube was adjusted to 25 mL by adding concentrated H_2SO_4 and mixed well. After 5 minutes, a portion of the solution was transferred to a cuvette and the absorbance was measured at 590 nm, using starch blank as a reference. A calibration curve was prepared with an aliquot (1 mL) of standard solution, containing 10, 20, 30, 40 and 50 mg/mL of propylene glycol. The hydroxypropyl group was calculated using equation (1):

$$\text{Hydroxypropyl groups (\%)} = \frac{\text{C x 0.7763 x 10 x F}}{\text{W}} \quad (1)$$

where C is the amount of propylene glycol in the sample solution determined from the calibration curve (mg/mL), F is the dilution factor and W is the weight of the sample (mg).

The molar substitution (MS) of the modified starch was calculated using equation (2):

$$\text{MS} = \frac{162\ \text{W}}{100 - (\text{M} - 1)W} \quad (2)$$

where W is the equivalent hydroxypropyl group in 100 g of starch and M is the molecular weight of C_3H_6O.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of native starch, hydroxypropyl starch, and hydroxypropyl starch nanoparticles were obtained using a Fourier Transform Infrared Spectrophotometer (FTIR) (SHIMADZU Model FTIR-8201PC). Dried starch powder samples were made into thin pellets with potassium bromide (KBr) and then scanned within the wavenumber ranges of 600 cm^{-1} and 4000 cm^{-1}.

Scanning Electron Microscopy (SEM)

The morphology of the samples was investigated using a scanning electron microscope (SEM) (JEOL Model JSM6390LA) at various magnifications. The samples were dropped on stainless steel plates, dried at room temperature, and coated with a layer of platinum using JEOL/ JFC-1600 Auto Fine Coater.

Transmission Electron Microscopy (TEM)

An appropriate amount of nanoparticles was dispersed in absolute ethanol and sonicated before they were dropped onto the fomvar-coated copper grids. TEM micrographs of the nanoparticles were obtained *via* a transmission electron microscopy (TEM) (JEOL Model 1230).

Swelling ratio

The swelling property of hydroxypropyl starch nanoparticles was studied by immersing dried hydroxypropyl starch (1g) in PBS solution of various pH values (1.2, 7.4 and 8.6) at 37°C. At predetermined time intervals (1-72 hours), samples were taken out from the PBS solution, dried with filter papers and weighed. The swelling ratio of hydroxypropyl starch nanoparticles was calculated using equation (3):

$$Swelling\ ratio\ (g/g) = \frac{Ws - Wd}{Wd} \quad (3)$$

where W_s is the weight of swollen hydroxypropyl starch nanoparticles and W_d is the weight of dried

starch nanoparticles

Loading of piperine onto hydroxypropyl starch nanoparticles

Piperine of various concentrations (0.1, 0.2, 0.3, 0.4 and 0.5 mg/L) was dissolved in 20 mL of absolute ethanol as a precipitating medium, then 1 mL of hydroxypropyl starch solution was added dropwise into the resulting solution and magnetically stirred for 30 minutes. Starch nanoparticles formed were separated from the reaction medium by centrifugation, and the concentration of piperine remained in the supernatant was quantified spectrophotometrically at a wavelength of 343 nm with a UV-vis spectrophotometer (Jasco V-630). The molar concentration of piperine was calculated from the absorbance value, based on a calibration curve of piperine in ethanol solution. The loading capacity of piperine for starch nanoparticles was calculated using equation (4):

$$Loading\ capacity\ (mg/mg) = \frac{[piperine]tot - [piperine]free}{weight\ of\ nanoparticles} \quad (4)$$

where $[piperine]_{tot}$ is the initial concentration of piperine used and $[piperine]_{free}$ is the concentration of piperine remained in the supernatant.

Drug release analysis

A predetermined amount of piperine loaded hydroxypropyl starch nanoparticles were dispersed in 20 mL of phosphate buffer saline (PBS) solution (pH 1.2, 7.4 and 8.6) at 37°C. At predefined time intervals, PBS was withdrawn from each of the release media and immediately replaced with the same volume of PBS solution. The molar concentrations of piperine in the supernatant were determined from the absorbance values measured at 655 nm against the calibration curve of piperine in PBS at pH 1.2, 7.4 and 8.6. The percentage of piperine released was measured according to equation (5):

$$Piperine\ released\ (\%) = \frac{[piperine]rel}{[piperine]load}\ x\ 100\% \quad (5)$$

where $[piperine]_{rel}$ is the concentration of piperine released at the time (t) and $[piperine]_{load}$ is the concentration of piperine being loaded onto the hydroxypropyl starch nanoparticles.

RESULTS AND DISCUSSIONS

Starch possesses a considerable amount of hydroxyl group that has anticipated to react with hydroxypropyl groups via etherification. As a result, some hydroxyl groups of the anhydroglucose unit of starch were replaced by hydroxypropyl groups. The reaction mechanism of the reaction between native sago starch and propylene oxide is shown in Fig. 1.

Molar substitution (MS) of hydroxypropyl starch

The effects of etherification conditions (% propylene oxide, temperature and reaction duration) on the MS of hydroxypropyl starch was investigated to study the efficiency of hydroxypropylation. As shown in Fig. 2a, it was found that the minimum and maximum MS was obtained at 0.003 and 0.13 when 5 and 25 % of propylene oxide were applied, respectively. Increasing the concentration of propylene oxide gives rise to higher alkalinity condition which could promote swelling by the ionizing starch hydroxyl group, which in turn yielded higher substitution [15]**.** At 30 % propylene oxide, the starch slurry gelatinized at room temperature and was not recoverable, therefore the reaction was

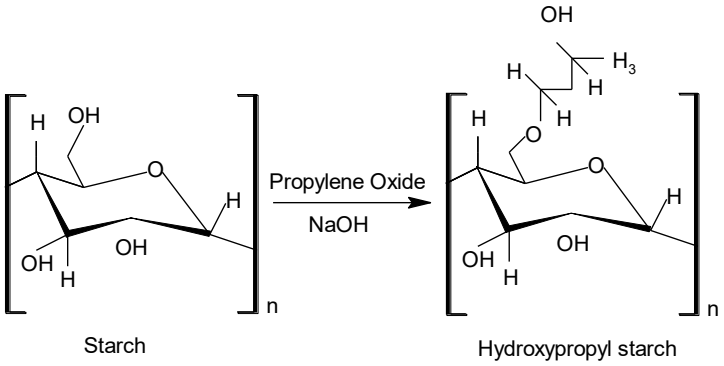

Fig. 1. Reaction scheme of hydroxypropylation of native sago starch to form hydroxypropyl starch.

not pursued. The effect of reaction temperatures on MS was investigated by heating the samples at various reaction temperatures.

Fig. 2b shows that hydroxypropylation did not occur at a temperature less than 30°C. Increasing reaction temperature of hydroxypropylation to around 40 to 50 °C showed a significant increase in MS, where MS 0.13 was obtained. However, when the temperature is further increased to 60°C, the MS was reduced to 0.07 which could be due to degradation of the starch. The effect of reaction durations on MS of hydroxypropyl starch is shown in Fig. 2c. There was no reaction occurred at a reaction time of fewer than 16 hours. After 16 hours reaction, hydroxypropyl starch with 0.05 MS was obtained. The maximum MS of 0.13 was obtained at 24 hours reaction time and when the reaction was pursued until 28 hours, the MS remained constant.

FTIR analysis

Fig. 3 shows the FTIR spectra of native starch, hydroxypropylated starch and hydroxypropyl starch nanoparticles analysed by FTIR. Fig. 3a showed the spectrum of native sago starch with absorption bands at 2942 cm^{-1} and 2887 cm^{-1} indicating the presence of CH band stretching. The band at 1638 cm^{-1} was attributed to the OH group (O-H from moisture in starch) and the band at 3258 cm^{-1} was due to the OH groups of starch molecules

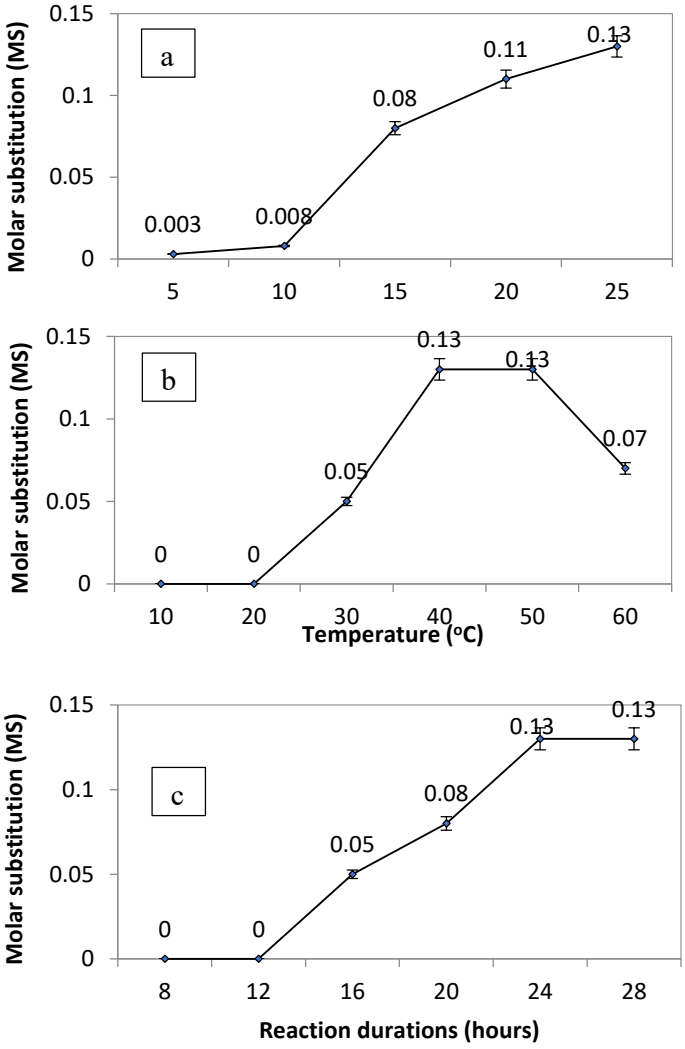

Fig. 2. Effect of synthesis conditions on the molar substitution (MS) of hydroxypropyl starch (a) propylene oxide concentration, (b) reaction temperatures and (c) reaction durations.

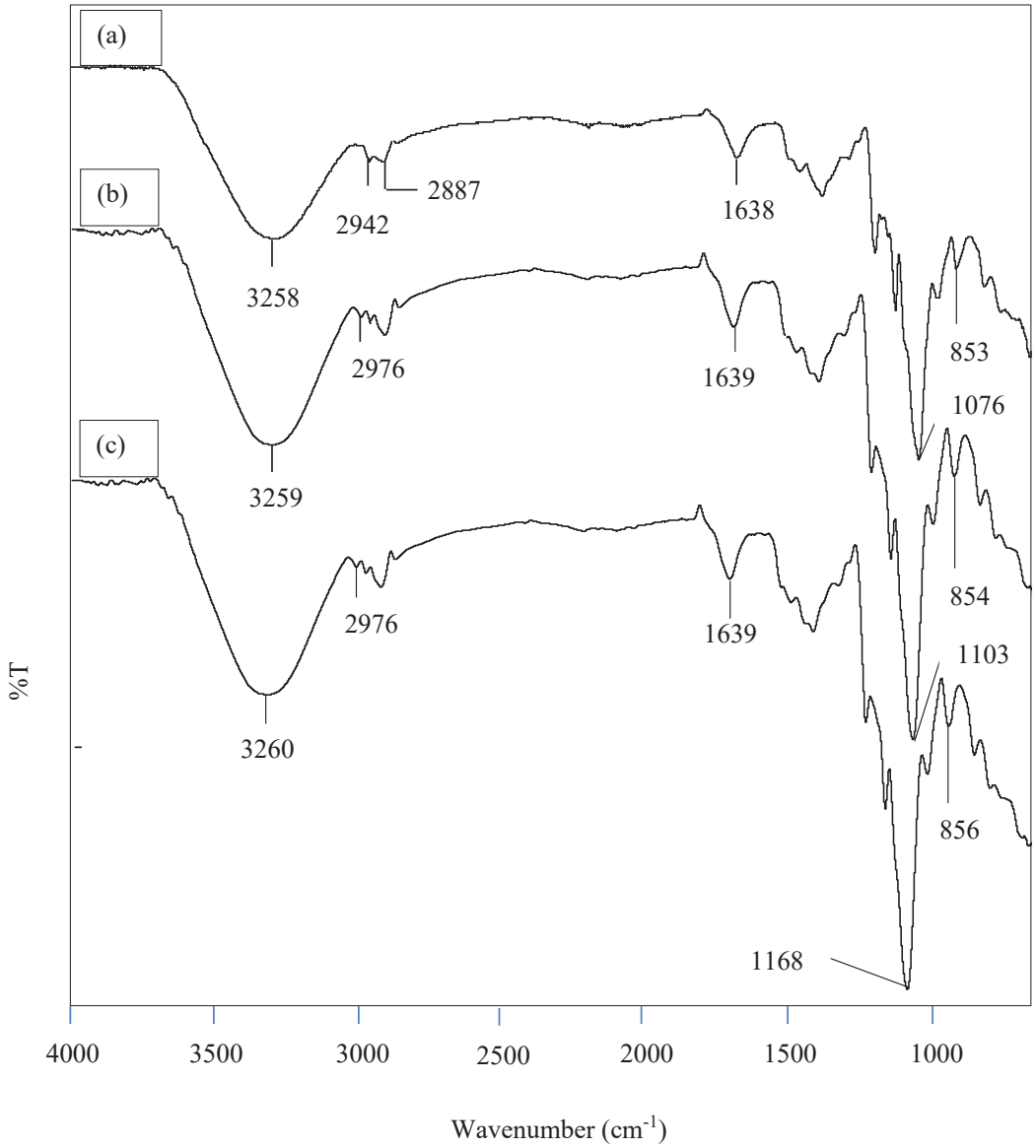

Fig. 3. FTIR spectra of (a) native starch, (b) hydroxypropyl starch and (c) hydroxypropyl starch nanoparticles.

[10] The peak at 1076-1068 cm^{-1} are mainly assigned to C-O stretch of C-O-H in starch [16]. After hydroxypropylation, a new characteristic absorption band was observed at 2976 cm^{-1} which corresponded to the asymmetric $CH(CH_3)$ stretching as shown in Fig. 3b. The appearance of the peak at 2976 cm^{-1} was a clear evidence of the successful hydroxypropylation of starch [17, 18]. Besides that, the absorption peak at 853-856 cm^{-1} attributed to C-O-C glycosidic bonds of anhydroglucose unit (AGU) of starch molecules was not degraded after hydroxypropylation [16]. The FTIR spectrum of hydroxypropyl starch nanoparticles (Fig. 3c) was similar to that of hydroxypropyl starch (Fig. 3b). This showed that nanoprecipitation process using ethanol as the precipitating medium did not break the bonds of the newly substituted groups.

Morphological study

As shown in Fig. 4a, the morphology of native sago starch granules was observed to be smooth and oval in shape with particle sizes around 20 to 45 µm. After nanoprecipitation, the size and shape of the nanoparticles are completely different from the native starch. Hydroxypropyl starch

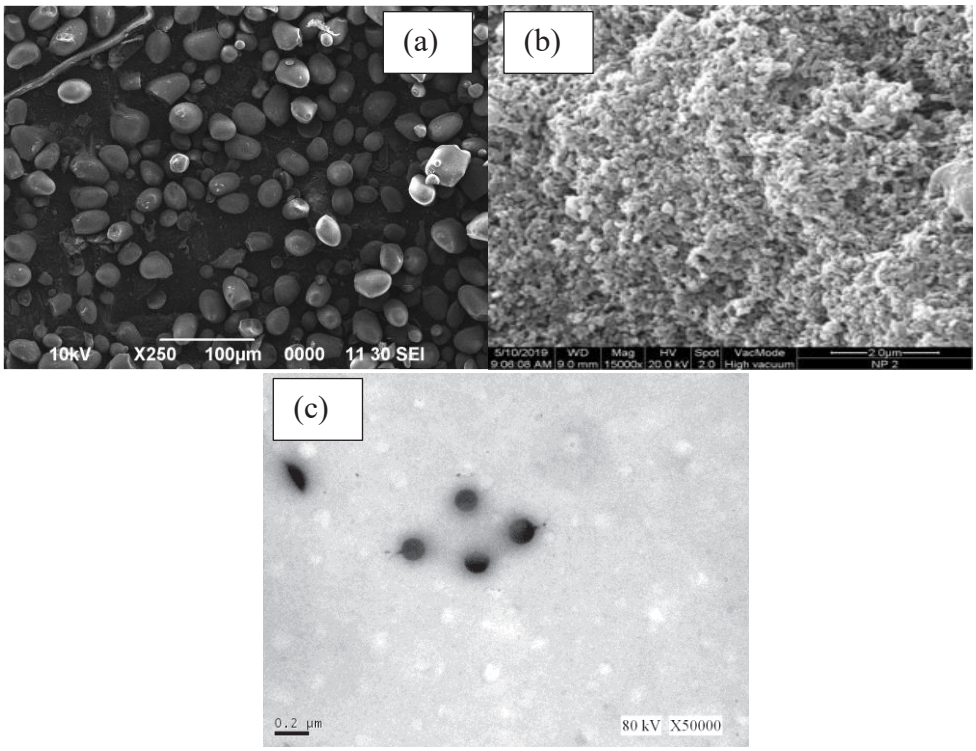

Fig. 4. (a) SEM images of native sago starch, (b) FESEM images of hydroxypropyl starch nanoparticles and (c) TEM images of hydroxypropyl starch nanoparticles.

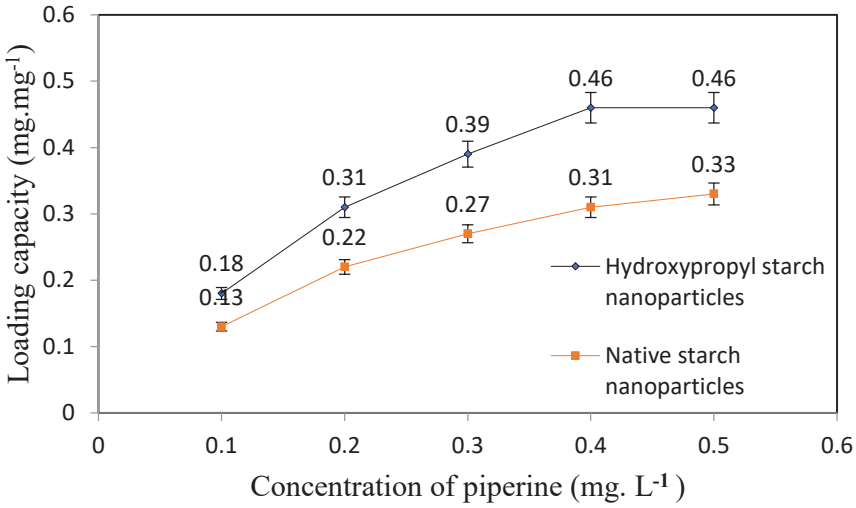

Fig. 5. Loading capacity of piperine onto native starch nanoparticles and hydroxypropyl starch nanoparticles.

nanoparticles are mainly spherical in shape with a mean particle sizes of 110 nm as shown in the SEM and TEM micrographs, respectively (Fig. 4b and Fig. 4c). During nanoprecipitation process, ethanol acts as the non-solvent to precipitate hydroxypropyl starch solution (solvent). Solvent interfacial deposition occurs at the interface of the solvent and non-solvent when the starch solution

diffused into the dispersive medium and gave rise to the formation of starch nanoparticles [19].

Piperine Loading Capacity

For comparison, the loading capacity of native starch nanoparticles and hydroxypropyl starch nanoparticles was investigated at different concentrations of piperine (0.1, 0.2, 0.3, 0.4 and 0.5 $mg.L^{-1}$) as shown in Fig. 5. The loading capacity of piperine onto native starch nanoparticles increased almost linearly from 0.13 to 0.33 $mg.mg^{-1}$ as the concentration of piperine increased from 0.1 to 0.5 $mg.L^{-1}$. Whereas, for hydroxypropyl starch nanoparticles, the loading capacity increased from 0.18 to 0.46 $mg.mg^{-1}$ when the concentration of piperine increased from 0.1 to 0.4 $mg.L^{-1}$. When the concentration of piperine was further increased to 0.5 $mg.L^{-1}$, the loading capacity remained constant. This may be due to the saturation of the adsorption sites of hydroxypropyl starch nanoparticles [20]. Overall, the hydroxypropyl starch nanoparticles were observed to have higher loading capacity compared to native starch nanoparticles.

Due to higher drug loading capacity demonstrated by the *in-situ* nanoprecipitation

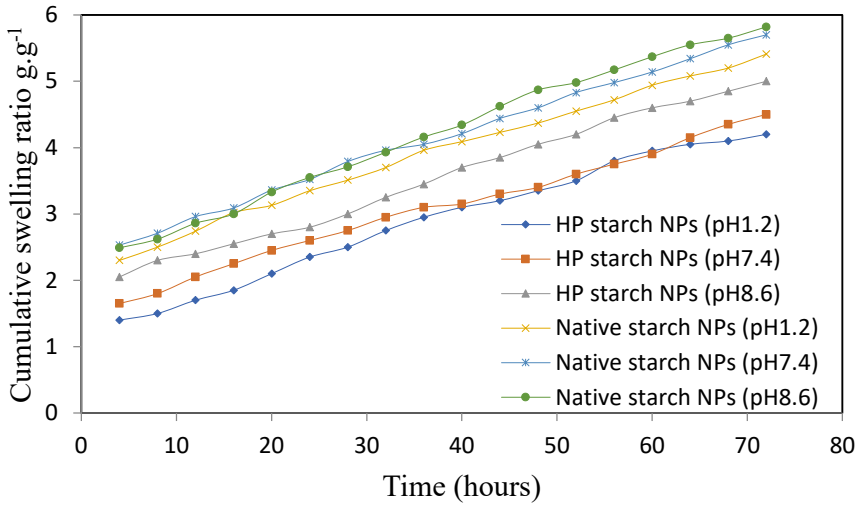

Fig. 6. Swelling ratios of native starch nanoparticles and hydroxypropyl starch nanoparticles in different pH of physiological media (1.2, 7.4 and 8.6) as a function of time.

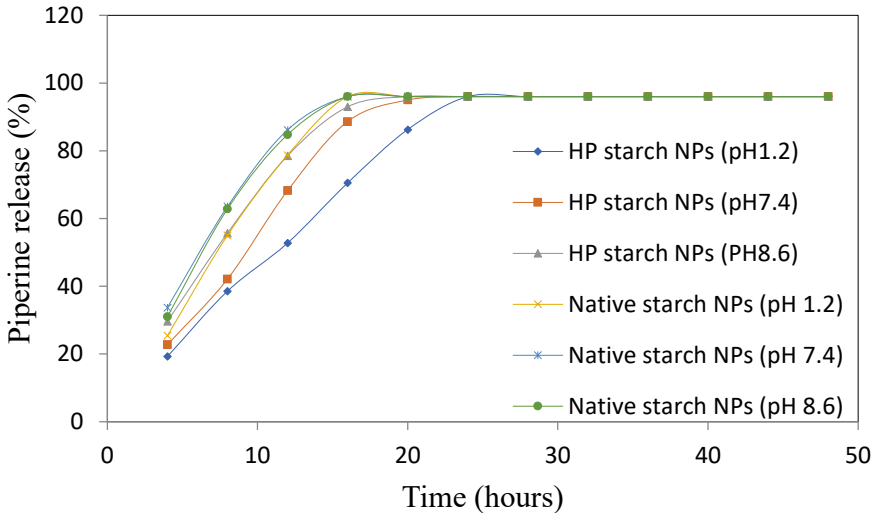

Fig. 7. Percentage of piperine released from native starch nanoparticles and hydroxypropyl starch nanoparticles in media of various pH.

technique compared to conventional methods, it was used in this research to load the piperine onto the nanoparticles [5]. Through etherification, the hydrophobicity of propylene oxide and the hydrophilicity of starch backbone are retained [21]. Adsorption of piperine onto hydroxyl propyl starch could occur through hydrophobic interactions. Piperine is hydrophobic thus are attracted by the hydrophobic surfaces of hydroxypropyl starch nanoparticles. During nanoprecipitation, the hydrophobic cores of hydroxypropyl starch nanoparticles were surrounded by hydrophilic outer shells, so the inner core served as nanocarrier for piperine, thus explained the observed higher loading capacity [21, 22].

Piperine release studies

The swelling behaviour of the native starch nanoparticles and hydroxypropyl starch nanoparticles and the release profiles of piperine from native starch nanoparticles and hydroxypropyl starch nanoparticles were investigated at various physiological pH values (1.2, 7.4 and 8.6) and the results were shown in Fig. 6 and 7, respectively. The piperine release profiles were observed to be dependent on the swelling behaviour of the starch nanoparticles. For native starch nanoparticles, piperine was completely released after 16 hours. This could be due to the higher swelling ratio (3.93, 4.25 and 4.22 gg^{-1}) at pH 1.2, 7.4 and 8.6, respectively. On the other hand, at pH 1.2, piperine was completely released from hydroxypropyl starch nanoparticles in a slow and constant manner within 24 hours. This observation could be due to the smaller swelling ratio (2.9 gg^{-1}) of hydroxypropyl starch nanoparticles in the acidic medium [20]. At pH 7.4 and 8.6 piperine was observed to slowly release from hydroxypropyl starch nanoparticles over the period of 16 and 12 hours, respectively. The hydrophobic nature of hydroxypropyl functional group has resulted in a relatively smaller swelling ratio of starch nanoparticles, which in turn, has caused the piperine to release at slower rates [8, 23].

CONCLUSION

Hydroxypropyl starch was successfully synthesized from native sago starch by hydroxypropylation reaction and nanoprecipitation method was used to synthesize nanoparticles from the hydroxypropyl starch. This study showed that hydroxypropyl starch nanoparticles have a higher loading capacity of piperine, lower swelling ratio, and slower drug release rates as compared to native starch nanoparticles. Moreover, the hydroxypropyl starch nanoparticles are derived from starch which is low cost, non-toxic, biocompatible and abundantly available, thus hydroxypropyl starch nanoparticles are very promising controlled release nanocarriers for piperine.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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