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Pharmaceutical Nanotechnology

Preparation and characterization of mucoadhesive polymer-coated nanoparticles

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Abstract

The transmucosal routes such as pulmonary, nasal and oral routes are most important and common routes for drug delivering to the body. However, peptide and protein drugs are degraded before they reach the blood stream and cannot cross the mucosal barriers. The mucoadhesive polymer-coated nanoparticles colloidal carriers can solve these problems. In the present investigation, mucoadhesive polymer-coated nanoparticles were prepared by emulsion polymerization process. A detailed preparation procedure of the mucoadhesive polymer-coated nanoparticles was provided. The parameters such as portion of the mucoadhesive polymers and concentration of the radical initiator were investigated. The resulting chitosan-coated nanoparticles colloids possessed positive surface charge, while poly(acrylic acid)-coated nanoparticles colloids and carbopol-coated nanoparticles colloids had negative surface charge. These nanoparticles were suitable for carrying hydrophilic protein or peptide drugs. Chitosan-coated nanoparticles were stable when pH value below 11, while poly(acrylic acid)-coated nanoparticles and carbopol-coated nanoparticles were stable under physiological pH conditions. Therefore, they are promising for transmucosal drug delivery.

Keywords: Nanoparticles; Mucoadhesive polymer-coated nanoparticles; Emulsion polymerization; Surface charge; Drug delivery

1. Introduction

Over the past few decades, there has been considerable interest in developing new routes, alternative to injection, for delivering the macromolecules such as proteins and peptides. Among them, the oral, nasal and pulmonary routes are most common and convenient routes for delivering drugs to body. However, peptide and protein drugs are degraded before they reach the blood stream and cannot cross the mucosal barriers (Prego et al., 2005). The mucoadhesive polymer-coated nanoparticles colloidal carriers are promising to solve these problems. In this study, we have focused on designing new types of nanoparticles adapted for transmucosal delivering drugs–mucoadhesive polymer-coated nanoparticles. They were prepared according to the emulsion polymerization (Lemarchand et al., 2004). More specifically, one was that methyl methacrylates polymerized in the presence of polysaccharide such as chitosan (Harish Prashanth and Tharanathan, 2003), the other one was that polymerization in the presence of acrylic acid derivatives (Lee, 2002). Through this emulsion polymerization, different surface charges of mucoadhesive polymer-coated nanoparticles were obtained.

Chitosan is a polysaccharide comprising copolymers of glucosamine and *N*-acetylglucosamine and can be derived by the partial deacetylation of chitin. It is a biodegradable, biocompatible and hydrophilic polymer of low toxicity (He et al., 1998). It is a material found in abundance in shells of crustacea such as lobsters, prawns and crabs. It is insoluble under alkaline and neutral conditions, but can react with inorganic and organic acids such as hydrochloric acid, lactic acid, acetic acid and glutamic acid under acidic conditions. It has OH and NH_2 groups that give rise to hydrogen bonding and these groups could act as nucleophilic agent to initiate the polymerization of methyl methacrylate, leading to an irreversible attachment between chitosan and methyl methacrylate through different multipoint linkages (Harish Prashanth and Tharanathan, 2003). Furthermore, the cationic polyelectrolyte nature of chitosan could interact with a negatively charged mucosal surface (Illum et al., 2001). It was also confirmed that coating liposomes with chitosan

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improved their adsorption to mucosal surfaces (Takeuchi et al., 1996).

Carbopol is a high molecular weight poly(acrylic acid) copolymer, loosely cross-linked with allyl sucrose. Poly(acrylic acid) (PAA) and its derivatives were not only as stabilizer but also as comonomers (Ishizu et al., 1997; Lee, 2002). They were reacted with methyl methacrylate through copolymerization. The mucoadhesive polymers could interact with the mucus glycoproteins by forming physical entanglements followed by hydrogen with sugar residues on the oligosaccharide chains, resulting in the formation of a strengthened mucus gel network, which allows the mucoadhesive system to remain adhesive for an extended period of times (Mortazavi, 1995). It was also showed that coating nanoparticles with them improved their mucoadhesion (Takeuchi et al., 2001; Kawashima et al., 2000; Ludwig, 2005).

Polymerization of methyl methacrylates in the presence of the above mucoadhesive polymers formed the mucoadhesive polymer-coated nanoparticles. These nanoparticles are not only suitable for carrying hydrophilic drugs but also provide mucoadhesion between mucosal epithelium and mucoadhesive polymers and to prolong the residence time of drug carriers at the drug absorption sites (Takeuchi et al., 2001).

The main goal of this study was to polymerize the mucoadhesive polymer-coated nanoparticles by emulsion polymerization method and to investigate various parameters influencing on the physical properties of the product particles during the polymerization. Different portions of mucoadhesive polymers and concentrations of the initiator varied to optimize the reaction conditions and to obtain a reproducible process for each mucoadhesive polymer. As a model drug, insulin was encapsulated into the nanoparticles. Finally, phenol red absorption was used to indicate that the poly(acrylic acid)-coated nanoparticles (PAANP) did not cause any damage to the intestine (Sakuma et al., 2002).

2. Materials and methods

2.1. Materials

Methyl methacrylate (M_W: 100.12) and ammonium persulfate (APS, M_W: 228.20) were purchased from Lingfeng Chemical Co. (Shanghai, China) and Anjian Chemical Co. (Shanghai, China), respectively. PAA $(C_3H_4O_2)_n$ ($n = 6$–60, M_W: 500–5000) was obtained from Jiangyan Chemical industries (Jiangsu, China). Carbopol 934PNF, Carbopol 974PNF and Carbopol 971PNF were kindly provided by PLEASE RECYCLE Co. (Shanghai, China). Chitosan (minimum 85% deacetylated) was purchased from Sigma Chemical Co. (USA). Phenol red ($C_{19}H_{14}O_5S = 354.38$) was obtained from Sanansi reagent limited Co. (Shanghai, China).

2.2. Preparation of nanoparticles

Poly(methyl methacrylate) (PMMA) nanoparticles were prepared according to the previous method (Zobel et al., 1999). Chitosan-coated, poly(acrylic acid)-coated, Carbopol 934PNF-coated, Carbopol 974PNF-coated, Carbopol 934PNF-coated nanoparticles were prepared by polymerizing methyl methacrylate in the presence of these mucoadhesive polymers using emulsion polymerization.

2.2.1. Preparation of PMMA homopolymer nanoparticles

The polymerization experiments were carried out in a round-bottomed flask containing known concentration of the monomer methyl methacrylate, in N_2 atmosphere, at 75 °C. The reaction mixture was stirred at 400–500 rpm, which helped in the formation of micelles in the mixture medium. The speed in this range had no remarkable effect on the rate of polymerization. The requisite amount of the initiator APS solution was carefully injected into the reaction mixture. The polymerization was completed after 24 h. These stock suspensions were purified by dialysis through a semi-permeable membrane with an exclusion diameter of 14,000 Da (Green Bird Science Development Limited Company, Shanghai, China). After purification, characterization was carried out.

2.2.2. Preparation of chitosan-coated nanoparticles (CSNP)

Graft copolymerization of methyl methacrylate onto chitosan was prepared according to the method (Harish Prashanth and Tharanathan, 2003).

CSNP were prepared by emulsion polymerization in a closed 100 ml flask. Chitosan was dissolved in 100 ml 1% acetic acid solution under magnetic stirring at 400–500 rpm, the pH value was adjusted to 4–5. One percent (w/v) of the monomer methyl methacrylate was dissolved in the above mixture at 75 °C and APS solution was added. The reaction was completed after 5 h. Different batches were prepared according to the following reaction conditions: (1) portions of chitosan varied over the range 0.15–1% (w/v) while the total monomer content and the concentration of the initiator APS kept constant; (2) concentrations of the initiator APS varied between 0.01% and 0.2% (w/v). The resulting nanoparticles suspensions were dialyzed as previously described for PMMA homopolymer nanoparticles.

2.2.3. Preparation of PAANP

PAANP were prepared by emulsion copolymerization of methyl methacrylate with PAA macromonomers in an aqueous solution (Ishizu et al., 1997).

The polymerization experiments were carried out in a round-bottomed flask containing 100 ml water. PAA was dissolved in water under stirring on a hotplate at 400–500 rpm. The pH value in the reaction medium was then adjusted to 2–3. One percent (w/v) of the monomer methyl methacrylate was dissolved in the above mixture at 75 °C. A 3% stock solution of APS in water was added. The reaction continued for 24 h. Different batches were prepared according to the following reaction conditions: (1) portions of PAA varied over the range 0–2.5% (w/v) while the total monomer content and the concentration of the initiator APS kept constant; (2) concentrations of the initiator APS varied between 0.01% and 0.2% (w/v). The resulting nanoparticles suspensions were dialyzed as previously described for PMMA homopolymer nanoparticles.

2.2.4. Preparation of carbopol-coated nanoparticles

The polymerization experiments were carried out in a round-bottomed flask containing 100 ml water. 2.4 mg carbopol was dissolved in water under stirring on a hotplate at 400–500 rpm, 1% (w/v) of the monomer methyl methacrylate was dissolved in the above mixture at 75 °C. A 3% stock solution of APS in water was added to give a final concentration of 0.0456% (w/v). The reaction continued for 24 h. Different batches were prepared according to different types of carbopol such as Carbopol 934PNF, Carbopol 974PNF and Carbopol 971PNF. The resulting nanoparticles suspensions were dialyzed as previously described for PMMA homopolymer nanoparticles.

2.3. Particle diameter and zeta potential of nanoparticles

The mean diameter and size distribution of the nanoparticles were measured by photon correlation spectroscopy (PCS) with particle sizing systems (PSS) (Nicomp 380/ZLS, Santa Barbara, CA, USA) in double distilled water and in buffer solutions with different pH values, respectively. All measurements were done at wavelength of 632.8 nm at 23 °C with an angle detection of 90°. Each sample was measured three times and the mean values recorded for two replicate samples.

Zeta potential of the nanoparticles was measured on PSS (Nicomp 380/ZLS). The samples were diluted with double distilled water. Each sample was repeatedly measured three times and the mean diameter values were for two replicate samples.

2.4. Morphology

Transmission electron microscopy (TEM) was used to observe the morphology of the nanoparticles. Samples were placed onto copper grill covered with nitrocellulose and they were negatively stained with phosphotungstic acid (PTA). They were dried at room temperature, and then examined by TEM (Hitachi, Japan).

2.5. Preparation of drug loaded nanoparticles

2.5.1. Preparation of insulin loaded PAANP

The PAANP colloids were dispersed in purified water at various concentrations. Insulin was dissolved in 0.01N hydrochloric acid solutions. They mixed together and the pH of the system was also adjusted to 5.4 with 0.01N NaOH. The mixture of nanoparticles and insulin was stirred slightly under magnetic stirrer at room temperature for 3 h.

2.5.2. Preparation of insulin loaded CSNP

The CSNP colloids were diluted with double distilled water and the final concentration of the particles varied from 1 mg/ml to 0.25 mg/ml. Insulin was dissolved in phosphate buffer solution (0.1 M PBS, pH 7.4) at the concentration of 0.6 mg/ml. They mixed together and the pH of the system was adjusted to 5.4 with 1N HCl. The mixture of nanoparticles and insulin was stirred slightly under magnetic stirrer at room temperature for 3 h.

2.5.3. Preparation of phenol red loaded PAANP

Phenol red was dissolved in isotonic phosphate buffered solution (pH 7.4, 0.01 mM) at a concentration of 2 mg/ml. PAANP colloids were at a concentration of 20 mg/ml. The nanoparticles colloids were mixed with an equivalent volume of phenol red solution. The mixture of nanoparticles and phenol red was stirred slightly under magnetic stirrer at room temperature for 3 h (Sakuma et al., 2002).

2.5.4. Entrapment efficiency

Each mixture was centrifuged at 15,000 rpm for 40 min at 25 °C to separate the free drug in the supernatant from the drug incorporated in the nanoparticles. Concentrations of insulin and phenol red in the supernatant were determined by Lowry Reaction method and by visible spectrometry at 550 nm, respectively. The amount of the drug incorporated in nanoparticles was calculated from the difference in drug concentrations between the supernatant and the original given concentrations (Sakuma et al., 2002). The entrapment efficiency was calculated according to the following equation:

$$\text{The entrapment efficiency} = \frac{\text{weight of the total insulin} - \text{weight of free insulin}}{\text{weight of total insulin}} \times 100\%$$

The loading efficiency was calculated according to the following equation (Jiang et al., 2005):

$$\text{The loading efficiency} = \frac{\text{weight of the total insulin} - \text{weight of free insulin}}{\text{weight of nanoparticles polymer}}.$$

2.6. Effect of PAANP on the absorption of phenol red

The experiments were performed as described previously (Kristl and Tukker, 1998). Rat intestine was obtained from male SD rats (240–250 g) under guidelines and legislative regulations on the use of animals for scientific purpose. After sacrification, the small intestine was immediately excised and placed into ice-cold, bubbled (carbogen, 95:5 O_2/CO_2) Ringer buffer. The colon 10 cm distal from the pyloric sphincter and jejunum were used, respectively. The tissue was rinsed with ice-cold standard Ringer buffer to remove luminal content and cut into segments opened along the mesenteric border and placed between the two EasyMount side-by-side diffusion chambers with an exposed tissue area of 0.785 cm^2. Attention was paid to avoid visible Peyer's patches. During the experiment, the tissue was bathed on both sides with Ring buffer containing 10 mM glucose at the serosal and 10 mM manitol at the mucosal side. After 20 min equilibration, phenol red loaded PAANP dispersed in Ring buffer was added to the mucosal side. The final volume of the solution in each compartment was kept at 5 ml. The concentration of the phenol red in the donor compartment was 100 μg/ml. Samples (250 μl) were withdrawn from the accept compartment at 30-min intervals up to 300 min and replaced with fresh Ring buffer containing 10 mM glucose. Then,

concentrations of phenol red in the samples were determined by visible spectrometry at 550 nm.

3. Results and discussion

The nanoparticles were formed through the mechanism as shown in Fig. 1. The polymerization was initiated by APS. Chitosan was reacted with methyl methacrylate through graft polymerization. PAA and its derivatives were not only as stabilizer but also as comonomers (Ishizu et al., 1997). They were reacted with methyl methacrylate through copolymerization. Because of the hydrophilic properties of mucoadhesive polymers compared with methyl methacrylate, the mucoadhesive polymers had hydrophilic properties. They could form nanoparticles in aqueous solution spontaneously. These mucoadhesive polymers might be on the surface of the nanoparticles.

3.1. Characterization of mucoadhesive polymer-coated nanoparticles

The resulting nanoparticles, when measured by PCS with PSS, demonstrated a unimodal size distribution. The Coefficient of variation varied from 0.047 to 0.548. The TEM photographs (Fig. 2) exhibited that the resulting nanoparticles were spherical and separated from each other.

3.1.1. Effect of chitosan on the CSNP

Diameter and surface charge of the CSNP were found to be dependent on portions of the mucoadhesive polymer chitosan (Fig. 3). PMMA nanoparticles had a negative charge of −7.07 mV. It was observed that the presence of chitosan during polymerization inverted the surface charge of nanoparticles with positive charge. When portions of chitosan increased from 0%

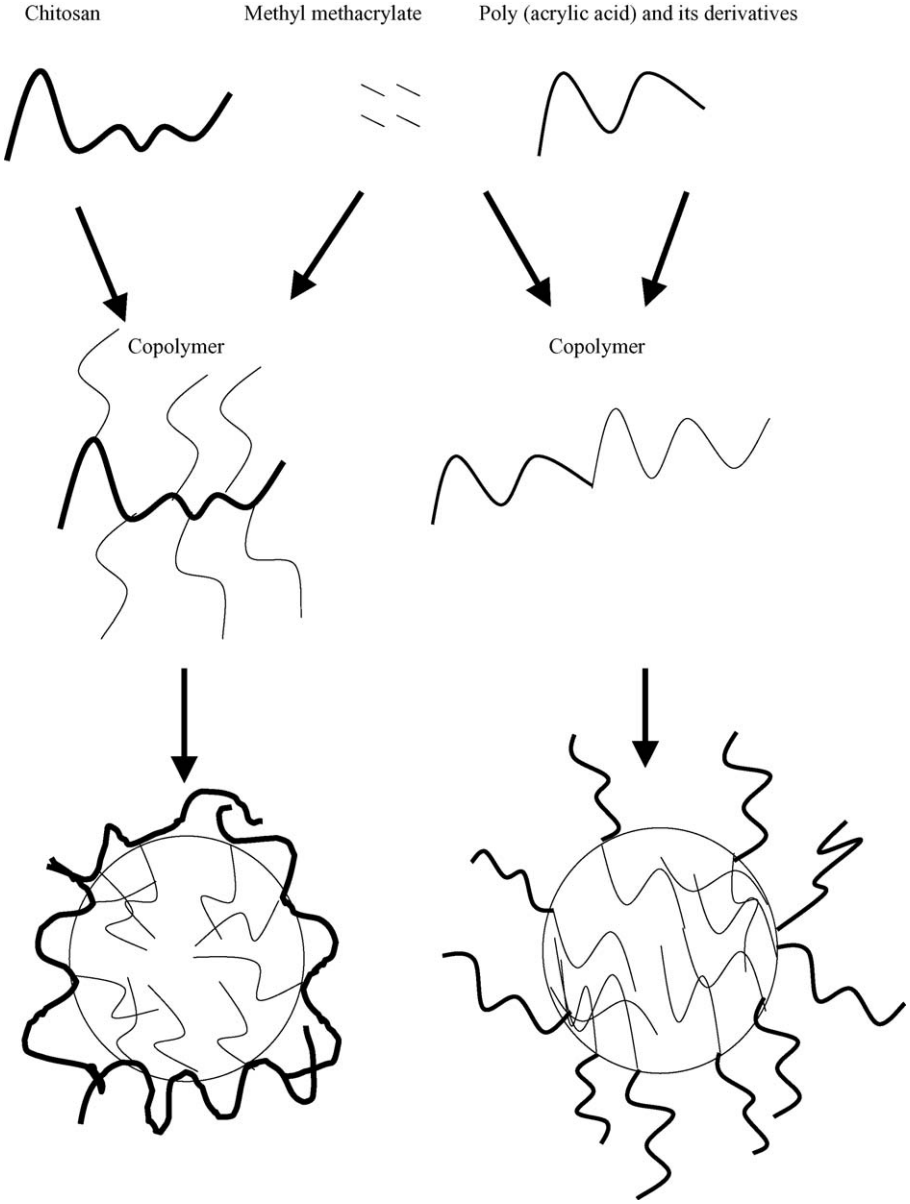

Fig. 1. Hypothetical conformation of the mucoadhesive polymer chains at the surface of nanoparticles depending on the mucoadhesive polymer applied for the synthesis of nanoparticles.

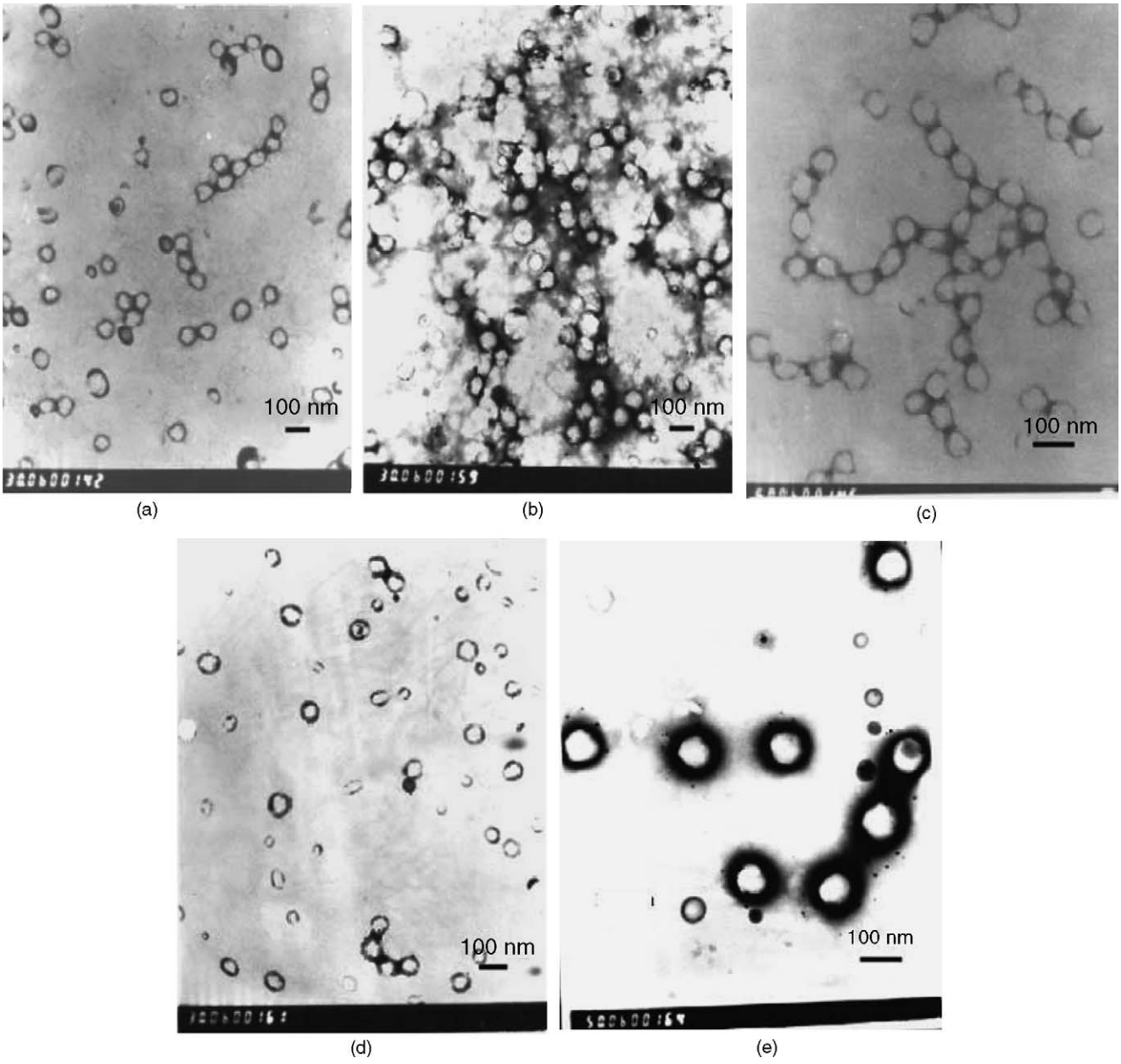

Fig. 2. (a) PMMA nanoparticles; (b) CSNP; (c) PAANP; (d) Carbopol 934PNF-coated nanoparticles; (e) Carbopol 974PNF-coated nanoparticles.

to 1% (w/v), the surface charge of nanoparticles was increased from −7.07 mV to 20.21 mV (Fig. 3). Diameters of the nanoparticles increased significantly with the increase of portions of chitosan from 0% to 0.1% (w/v). When portions of chitosan increased from 0.1% to 0.5% (w/v), the nanoparticles diameter was reduced from 345 nm to 139 nm. When portions of chitosan were increased from 0.5% to 1% (w/v), the particles diameters became larger (Fig. 3).

Amino groups of chitosan were partly positively charged. Due to the increase of the positively charged amino groups, the surface charge of the CSNP increased. The increased diameters of nanoparticles, could be due to slight aggregation caused by the reduction of negative surface charge and the following reducing repulsion forces between particles. In fact, with the increase of portions of chitosan from 0.1% to 0.5% (w/v), nanoparticles diameters were reduced. This is due to two aspects: increasing surface hydrophilicity and increasing surface charge repulsion. At portions of chitosan above 0.5% (w/v), the particle diameters increased greater. The increased particles diameters were attributed to the increased chitosan viscosity (Kawashima et al., 2000). Based on these results, the formulation containing 0.5% (w/v) of chitosan was selected for further studies.

3.1.2. *Effect of PAA on the PAANP*

Diameter and surface charge of the PAANP were found to be dependent on portions of the mucoadhesive polymer PAA (Fig. 4). With the increase of the portions of PAA from 0% to 2.5% (w/v), the surface charge of the PAANP was reduced from −7.07 mV to −33.45 mV (Fig. 4). In terms of the particles diameters, when portions of PAA were increased from 0% to

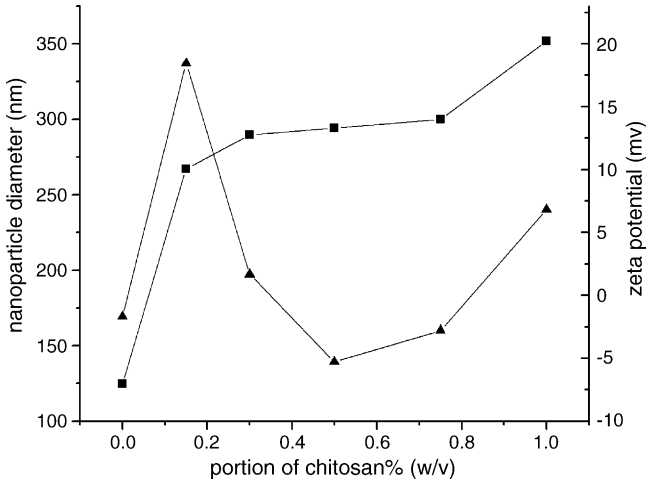

Fig. 3. Nanoparticle diameter and zeta potential of CSNP vs. the portion of chitosan: (▲) nanoparticle diameter of CSNP (mean ± S.D., $n = 3$) and (■) zeta potential of CSNP.

0.4% (w/v), particles diameters reduced from 169 nm to 123 nm. Continuing to increase the portions of PAA from 0.4% to 2.5% (w/v), particles diameters were increased greater (Fig. 4).

Carboxylic groups of PAA were partly negatively charged. Due to the increase of the negatively charged carboxylic groups, the surface charge of the PAANP was reduced. When portions of PAA were increased from 0% to 0.4% (w/v), the decreased diameters of nanoparticles could also be attributed to aspects: increasing hydrophilicity and surface charge repulsion. When the portions of PAA were increased from 0.4% to 2.5% (w/v), the increased diameters of particles were mainly due to the increase of the viscosity of PAA.

By comparing the zeta potential of the nanoparticles which were prepared with pure methyl methacrylate with the nanoparticles that were prepared with methyl methacrylate and mucoadhesive polymers, the formation of polymer layers on the surface of the nanoparticles was also confirmed.

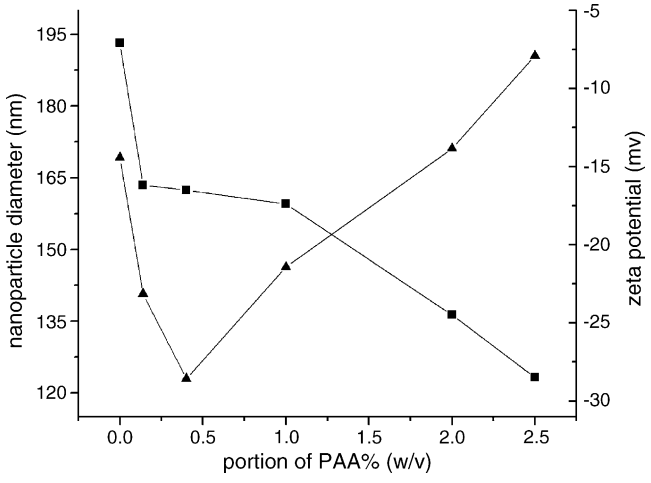

Fig. 4. Nanoparticle diameter and zeta potential of PAANP vs. the portion of PAA: (▲) nanoparticle diameter of PAANP (mean ± S.D., $n = 3$) and (■) zeta potential of PAANP.

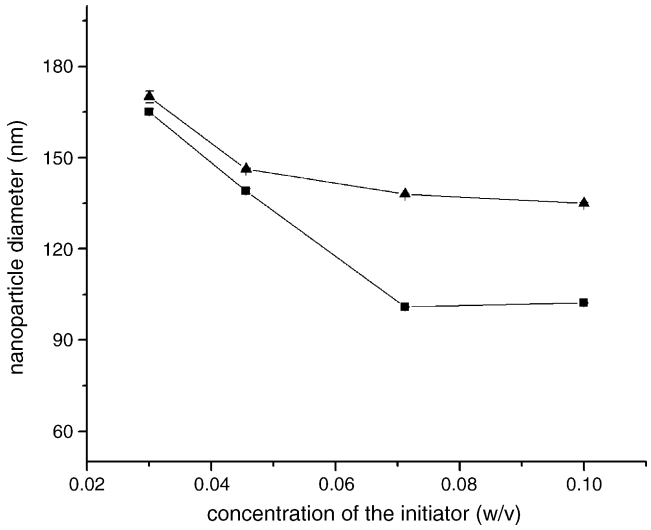

Fig. 5. Effect of the concentration of the initiator APS on the diameter of the resulting nanoparticles: (▲) CSNP (mean ± S.D., $n = 3$) and (■) PAANP (mean ± S.D., $n = 3$).

3.1.3. Effect of the initiator APS

Increasing the concentrations of the initiator APS up to 0.2% at a fixed concentration of 1% (w/v) monomer methyl methacrylate and definite temperature, the diameters of the resulting nanoparticles decreased slightly (Fig. 5). This is because higher APS concentrations increased the number of the radicals resulting in a reduction in the molecular weight of the copolymers. In one of the previous studies, a strong correlation between particle diameters and molecular weights was observed for sulfopropyl-methacrylate copolymer nanoparticles (Langer et al., 1996). Hence, it is very likely that the increase of initiator concentration was attributed to the smaller nanoparticles diameter. However, the particle diameter did not change much. It is assumed that in this situation more polymer molecules were required to form a single particle in order to achieve an even particle diameter.

3.1.4. Effect of carbopol on the nanoparticle diameter and zeta potential

The mean particle diameter and zeta potential of carbopol-coated nanoparticles were shown in Table 1. The influence of carbopol on the nanoparticle diameter and zeta potential was not further investigated.

Table 1
The mean particle diameter and zeta potential of Carbopol-coated nanoparticles

Formulation	Nanoparticle diameter (nm)	Zeta potential (mV)
Carbopol 934PNF-coated nanoparticles	174.7 ± 38.5	−18 ± 0.08
Carbopol 974PNF-coated nanoparticles	103.4 ± 47.1	ND[a]
Carbopol 971PNF-coated nanoparticles	197.5 ± 23.3	−16.6 ± 0.04

Data shown are the mean ± S.D. ($n = 3$).
[a] Not determined.

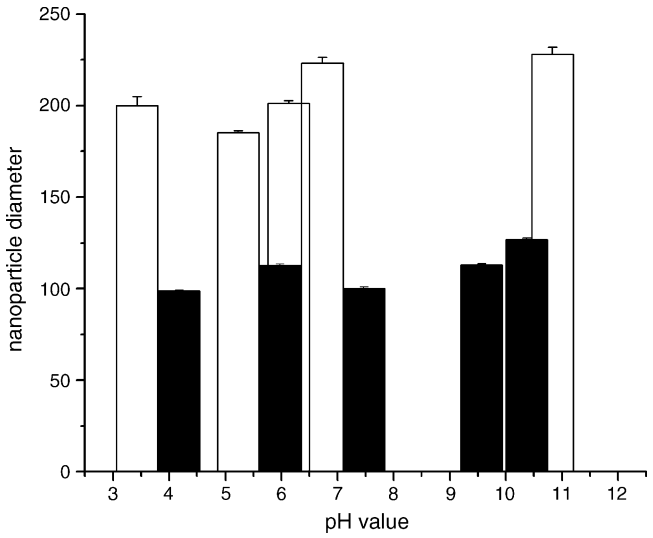

Fig. 6. Effect of pH value on the diameter of the mucoadhesive-coated nanoparticles. Black bars represent the PAANP and white bars represent the CSNP (mean ± S.D., $n = 3$).

3.2. Effect of pH values on the nanoparticle diameters

A series of pH values solutions were prepared in order to investigate the effect of the pH values on the formed nanoparticles. The obtained nanoparticles were incubated in different pH values (pH 3.8, 4.6, 5.6, 6.5, 7.1, 9.2, 10.0 and 11.2) solutions (Hu et al., 2002). Fig. 6 showed that the polymer-coated nanoparticles diameters were influenced slightly by the above pH values. They were stable in these conditions except that CSNP aggregated as pH value was above 11, so these particles might be suitable for oral drug delivery under physiological conditions, e.g. insulin oral administration.

3.3. Entrapment efficiency of nanoparticles

Table 2 showed that the entrapment efficiency was decreased with the increase of the weight ratio of the drug to polymer. The lower the weight ratio was, the higher the entrapment efficiency was. The loading efficiency was increased dramatically from 8.54% to 16.26% for PAANP when the weight ratio of the drug to polymer was increased from 1:10.0 to 1:4.0, while the weight ratio was increased from 1:4.0 to 1:2.5, the loading efficiency was increased slightly.

There was the same situation for CSNP.

This may be because at lower weight ratio of the drug to polymer, there were lots of insulin molecules absorbed on the surfaces of nanoparticles; at higher weight ratio of the drug to polymer, nanoparticles surfaces became almost saturated with insulin. There were only few insulin molecules absorbed onto the surfaces of nanoparticles. Therefore, the loading efficiency of insulin almost did not change with the increase of weight ratio of drug to polymer.

These nanoparticles were composed of hydrophobic backbones and hydrophilic branches. The insulin was encapsulated mainly through electrostatic interaction between the mucoadhesive polymers chains and insulin. And also there were other interactions such as hydrogen bonding between insulin and the hydrophilic mucoadhesive polymers. Therefore, insulin molecules might distribute between chains of mucoadhesive polymers. Generally speaking, insulin was absorbed onto the surface of nanoparticles.

In order to increase the loading efficiency of nanoparticles, the pH value of the final system should be adjusted to 5.4, which is insulin pK_a. When the system pH value exceeds 5.4, the insulin will have negative charge. While at this pH, the CSNP colloids have partly positive charge. Due to the surface electrostatic interaction, the negative charge insulin will be bound on the surface of the CSNP. In the case of PAANP, the insulin should be prepared when the pH below pK_a, at which the insulin will have positive charge. While at the same pH, the PAA on the surface of the nanoparticles will not have charge. There will not be surface electrostatic repulsion between insulin and PAANP.

Table 2
Formulation design, drug entrapment efficiency and loading efficiency of insulin-loaded nanoparticles

Batch	Formulation (drug to polymer)[c]	Entrapment efficiency (%)	Loading efficiency (%)
PAANP-1[a]	1:10.0	85.34 ± 1.12	8.53 ± 1.12
PAANP-2[a]	1:4.0	65.03 ± 0.34	16.26 ± 0.11
PAANP-3[a]	1:2.5	43.32 ± 1.20	17.33 ± 0.31
CSNP-1[b]	1:10.0	73.54 ± 2.01	7.35 ± 0.01
CSNP-2[b]	1:4.0	71.64 ± 0.54	17.91 ± 0.02
CSNP-3[b]	1:2.5	52.53 ± 0.98	21.01 ± 0.01

Data shown are the mean ± S.D. ($n = 3$).
[a] PAA/methyl methacrylate = 1/1 (weight ratio).
[b] Chitosan/methyl methacrylate = 0.5/1 (weight ratio).
[c] Weight ratio.

3.4. The effect of PAANP on the absorption of phenol red

Figs. 7 and 8 showed that the absorption of phenol red was not improved by PAANP at the colon and jejunum. The strongly

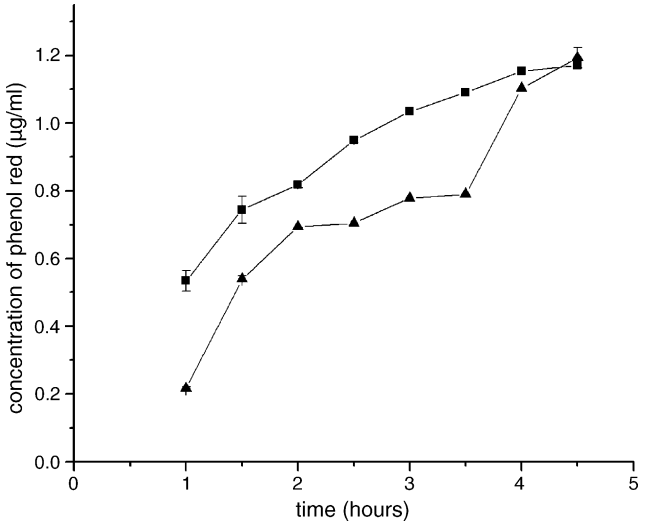

Fig. 7. Effect of the concentration–time profiles of PAANP on the absorption of phenol red at the colon: (▲) a mixture of nanoparticles and phenol red and (■) phenol red only. Each value represents mean ± S.D. of two experiments.

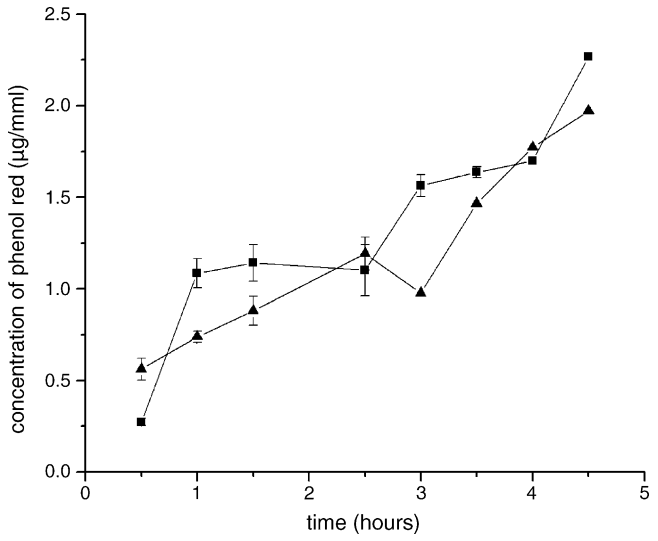

Fig. 8. Effect of the concentration–time profiles of PAANP on the absorption of phenol red at the jejunum: (■) a mixture of nanoparticles and phenol red and (▲) phenol red only. Each value represents mean ± S.D. of two experiments.

acidic phenol red having a sulfonic acid group was not interacted with non-ionic PAANP (Sakuma et al., 2002).

The absorption of phenol red was from solution. The main mechanism of enhancement absorption was the alteration of GI membrane permeability. If the adhesion of polymer particles on the mucin layer and subsequent dislodgment from this lining will affect the continuity and thickness of the mucin layer and consequently, it will also affect the rate and the amount of absorption of phenol red. It is known that one of the main functions of mucin layer is to control the diffusion process of molecules across this viscous layer.

If this layer is damaged, destroyed or thinned, the absorption of phenol red is greatly increased (Tur et al., 1997). The poor absorption of phenol red indicated that PAANP did not cause damage in the intestine.

4. Conclusions

The mucoadhesive polymer-coated nanoparticles could be developed through polymerizing methyl methacrylates in the presence of mucoadhesive polymers. The resulting nanoparticles suspension could incorporate the hydrophilic drugs greatly due to the hydrophilicity on the surface of the nanoparticles. They possessed mucoadhesive polymers, which interacted with mucus to prolong the residence time of drug carriers at the drug absorption sites and protected the entrapped peptide drugs from enzymatic degradation until they were absorbed. Therefore, the bioavailability of drug may be improved. Another aspect is that these nanoparticles were stable under physiological conditions. Therefore, they are promising for transmucosal drug delivery.

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