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Research paper

The pH-controlled dual-drug release from mesoporous bioactive glass/polypeptide graft copolymer nanomicelle composites

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Abstract

Dual-drug delivery systems are investigated for combined therapy with drugs having distinct therapeutic effects. However, the majority of current dual-drug delivery systems are designed for simultaneous release of two different drugs; the release of each individual drug cannot be controlled. In this study, we have demonstrated a novel dual-drug delivery system based on mesoporous bioactive glass/polypeptide graft copolymer nanomicelle composites. Water-soluble gentamicin and fat-soluble naproxen were used as model drugs in the study of this system. A pH-controlled release of individual drugs was achieved by the predominant release of gentamicin from mesoporous bioactive glass in an acid environment and fast release of naproxen in an alkaline environment from polypeptide nanomicelles. Our results suggest that the mesoporous bioactive glass/PBLG-g-PEG nanomicelle composites can be used as a dual-drug delivery system, and that the individual drug release can be controlled by the pH of the surrounding environment.

Keywords: Drug delivery; Mesoporous materials; Polypeptide; Bioactive glass; Controlled release

1. Introduction

Hydrophilic and hydrophobic drugs are designed to treat different diseases, and these drugs need to be selectively absorbed by different material systems according to their solubilities [1,2]. In addition, the delivery of drugs from biomaterials should be performed in a controlled manner to enhance the therapeutic effect and prevent deleterious side-effects. The majority of the current drug delivery systems can only load a single drug since each drug has different properties such as solubility and hydrophilicity, and generally require the use of multiple carriers or solvents. Recently, dual-drug delivery systems have been an area of major study in order to provide combined therapy with drugs having distinct therapeutic effects [3–5]. However, these delivery systems are designed only for the simultaneous release of two different drugs, and the release of each drug cannot be controlled. In addition, the drug release process is determined by the manner in which the drugs are taken. For example, drugs given by oral administration first go through the stomach where the pH is about 2.0, and then travel to the intestine where the pH increases to weak acidic or neutral. Therefore, in this situation, an ideal dual-drug release system will be expected to release the first drug in low pH environment, followed by the release of the second drug in neutral pH environment. In this study, we designed a mesoporous bioactive glass/nanomicelle composite drug delivery system, which has demonstrated the ability to release two different drugs

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and the release of each drug could be controlled by different pH environments.

Core-shell-type nanoparticles composed of biodegradable block copolymer have been investigated as sustained and controlled drug delivery systems [6–12]. The polypeptide copolymers are non-toxic, non-immunogenic, and will not accumulate in the host over the long-term [13], which meet the requirements for an effective drug delivery system. The core-shell type micelles will stay water-soluble during the encapsulation of water-insoluble drugs, which can increase the in vivo absorption of the drugs. Recently, mesoporous bioactive glasses have been investigated as drug delivery systems due to their adjustable pore diameter and high specific surface area [14–20]. Further study has shown that the gentamicin release from this mesoporous bioactive glass was pH dependent [21].

Herein, we prepared a dual-drug delivery system (DDDS) based on the mesoporous bioactive glass/polypeptide graft copolymer nanomicelle composite. Two different kinds of drugs, a water-soluble gentamicin and a fat-soluble naproxen, were loaded in this system. Gentamicin (Fig. 1A) is an aminoglycoside antibiotic used to treat infections caused by many different types of bacteria. Naproxen (Fig. 1B) is a non-steroidal anti-inflammatory drug, and is used to reduce pain, inflammation, and stiffness. A pH-controlled dual-drug release was achieved based on the predominant release of gentamicin from bioactive glass in an acidic environment, followed by a fast release of naproxen in an alkaline environment from polypeptide nanomicelles.

2. Materials and methods

2.1. Materials

Tetraethyl orthosilicate (TEOS, 98%), triethyl phosphate (TEP), calcium nitrate ($Ca(NO_3)_2{\cdot}4H_2O$, 99%), hydrogen chloride (HCl, 36–38%), and poly(vinyl pyrrolidone) (PVP, K30, average molecular weight 45, 000) were purchased from Sinopharm Chem. Reagents. Co. Ltd. Surfactant pluronic P123 (EO_{20}–PO_{70}–EO_{20}) was purchased from JIDA Co. (China). Polyethylene glycol monomethylether (mPEG) ($M_w = 350$), methoxypolyethylene glycol amine ($M_w = 5000$), and pyrene were purchased from Sigma Inc. The antibiotic gentamicin sulfate (GS, powder) was purchased from PUKANG Co. (China). Naproxen sodium was purchased from Sigma Inc. All materials were used as received without further purification.

2.2. Synthesis of mesoporous bioactive glass (MBG) and polypeptide copolymers

MBG was synthesized by a two-step acid-catalyzed self-assembly process combined with hydrothermal treatment using P123 (EO_{20}–PO_{70}–EO_{20}) as a template [21]. To begin preparation, 4.0 g of P123 was dissolved in 120 ml of 2 M HCl and 30 ml of distilled water solution while stirring at 35 °C in a water bath until the solution became clear. TEOS, TEP and $Ca(NO_3)_2{\cdot}4H_2O$ (molar ratio: P123/TEOS/TEP/$Ca(NO_3)_2{\cdot}4H_2O$ = 0.017:1:0.099:0.195) were then added into the solution. The mixture was stirred at 35 °C for 12 h, and then was hydrothermalized at 100 °C for 48 h. Without any filtering or washing, the resulting precipitate was directly dried at 100 °C for 20 h in air. The as-synthesized powders were calcined at 650 °C in air for 6 h in order to remove the organic structure-directing agents completely. The heating rate for the calcination was fixed at 1 °C/min.

Poly(γ-benzyl-L-glutamate)-poly(ethylene glycol) graft copolymer (PBLG-g-PEG, Fig. 2) was prepared by the ester exchange reaction of PBLG with polyethylene glycol monomethylether (mPEG) in 1,2-dichloroethane according to the method described in our previous work [22]. Micelles of PBLG-g-PEG were prepared by first dissolving PBLG-g-PEG in a mixed solvent of tetrahydrofuran (THF)/*N*,*N*dimethylformamide (DMF) [30/70, v/v] in a volumetric flask. The solution was then stirred at room temperature until the polymer was completely dissolved. The polymer concentration was maintained at 0.25 g/L. The solution was dialyzed against deionized water using cellulose dialysis tubing (type: Membra-cel, provided by Serva Electrophoresis GmbH, 3500 molecular weight cut-off) to form micelles and remove the organic solvents for about 48 h at room temperature. The deionized water was exchanged at intervals of 3–4 h. The solution obtained was diluted with deionized water to the desired concentration and then equilibrated at room temperature for 3–4 days before measurements. The polymer concentration for all of the solutions refers

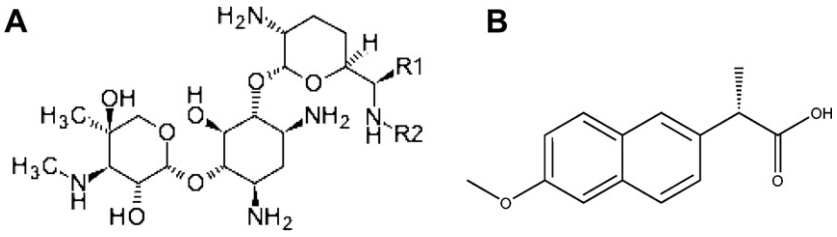

Fig. 1. (A) Chemical formula of gentamicin and (B) chemical formula of naproxen.

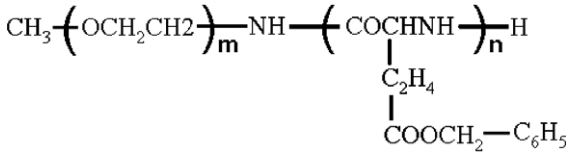

Fig. 2. Chemical formula of poly(γ-benzyl-L-glutamate)-poly(ethylene glycol) graft copolymer (PBLG-g-PEG).

to the weight percentage of the total copolymers in the water.

2.3. Preparation of the dual-drug delivery system based on the mesoporous bioactive glass/PBLG-g-PEG nanomicelle composite

Firstly, gentamicin sulfate (GS) was encapsulated into the MBG. 0.5 g of MBG powder was added to 50 ml of a gentamicin solution (10 mg/ml) and stirred for 24 h. The amount of loaded gentamicin was measured by determining the gentamicin concentration difference in the loading medium before and after loading. Secondly, naproxen sodium (Nap) was entrapped into the PBLG-g-PEG nanomicelles. The formation of core-shell type micelles and drug loading procedure were carried out by a diafiltration method. PBLG-g-PEG and naproxen were dissolved in DMF/THF (7/3, v/v). The solution was stirred at room temperature until all components were completely dissolved. To form core-shell type micelles and remove free drugs, the solution was dialyzed using a dialysis tube with molecular cut-off 3500 g/mol for 60–72 h, and distilled water was exchanged at intervals of 3–4 h. Finally, the GS-loaded MBG was added into the Nap-loaded PBLG-g-PEG nanomicelle solution. The mixture was gently stirred at room temperature. The obtained dual-drug loaded composite was washed using deionized water. The mixture was then freeze-dried. The final amount of drug loading was measured by the depletion method.

2.4. Characterization

The powder X-ray diffraction (XRD) patterns were obtained on a Rigaku D/MAX-2550V diffractometer at 40 kV and 100 mA (Cu Kα radiation). The morphology of the MBG and polypeptide copolymers was analyzed using scanning electron microscopy (SEM, JSM-6700F, Japan) working at 15 kV, and transmission electron microscopy (TEM, JEM2010, Japan) working at 200 kV. The UV/vis absorbance spectra were measured using a Shimadzu UV-3101PC spectroscope. N_2 adsorption–desorption isotherms were obtained on micromeritics Tristar 3000 poreanalyzer at 77 K under continuous adsorption condition. Brunauer–Emmett–Teller (BET) and Barrett–Joyner–Halenda (BJH) analyses were used to determine the surface area, pore size and pore volume of the mesoporous bioactive glasses.

2.5. In vitro drug release study

The samples (50 mg) were immersed into the release medium (10 ml) with different pH values (pH 1.2 or 10.0) at 37 °C with agitation. At given time intervals, 5 ml of the release medium was removed, using a syringe, for analysis. The same volume of fresh release medium was used to replace what was removed.

The extracted medium was diluted to a desired concentration with release medium and analyzed by UV/vis spectroscopy. Gentamicin release measurements were carried out by mean of UV/vis spectroscopy proposed by the Sampath and Robinson, with a slight modification by Zhang et al. [23]. The analytical method of Naproxen concentration was according to the P.R. Rege's measurement [24]. A calibration curve (correlation coefficient > 0.99) was made for each set of measurements and determined by taking absorbance vs. drug (gentamicin and naproxen) concentration.

3. Results

The detailed synthesis, characterization, and drug release behavior of mesoporous bioactive glasses have been reported in our recent paper [21]. Fig. 3A shows an SEM image of mesoporous bioactive glasses with the composition of 77 wt% SiO_2, 9 wt% P_2O_5, and 14 wt% CaO. The results of BET and BJH analysis showed that the specific surface area was 424.3 m^2/g, and the average pore diameter was 6.9 nm. The highly ordered mesoporous array under high-resolution TEM (HRTEM, Fig. 3B) observations

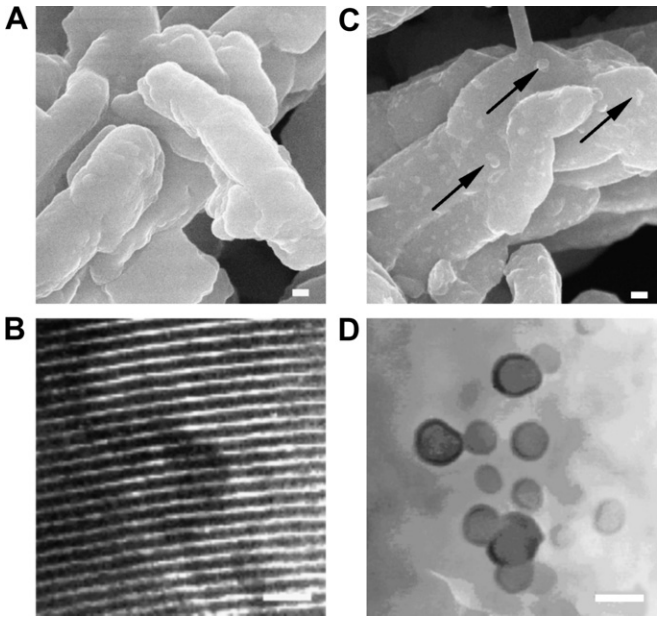

Fig. 3. (A) FESEM images of mesoporous bioactive glass; (B) HRTEM image of MBG, which showed well-ordered mesoporous structure; (C) mesoporous bioactive glass/PBLG-g-PEG nanomicelle composite (The arrows indicated the polypeptide.); and (D) TEM image of PBLG-g-PEG/Nap (bar: 100 nm).

suggested that MBG had a uniform, well-defined mesoporous structure. Polypeptide copolymer nanomicelles were synthesized by the ester exchange reaction of poly(γ-benzyl-L-glutamate) (PBLG) with polyethylene glycol (PEG) according to the method described in our previous report [22]. The micrograph of mesoporous bioactive glass/PBLG-g-PEG nanomicelle composites is shown in Fig. 3C. It is observed that many sphere-like micelles with a size of 50–100 nm were uniformly distributed on the surface of MBG while the surface of the mesoporous bioactive glasses was smooth before compounding. The TEM micrograph (Fig. 3D) demonstrated that PBLG-g-PEG nanomicelles loaded with Nap had a spherical shape, and the morphology of drug-loaded nanomicelles was largely conserved after compounding.

As shown in Table 1, the GS loading in MBG and Nap loading in PBLG-g-PEG before compounding were 405 $mg_{(GS)}/g_{(MBG)}$ and 86 $mg_{(Nap)}/g_{(PBLG\text{-}g\text{-}PEG)}$, respectively. The amount of drug loading decreased to 321 $mg_{(GS)}/g_{(MBG)}$ and 76 $mg_{(Nap)}/g_{(PBLG\text{-}g\text{-}PEG)}$ after PBLG-g-PEG/Nap compounded with MBG/GS. This was attributed to the loss of some drug molecules from the system during the compounding and washing processes.

Fig. 2 shows the cumulative release of GS and Nap from the DDDS at pH 1.2 (Fig. 4A) and pH 10.0 (Fig. 4B). The Nap release from the DDDS at pH 1.2 was considerably slow and reached 32% in 10 days. On the contrary, the GS release was much faster under this condition, with approximately 100% release of the drug within 2 h. However, the release behavior of the DDDS reversed at pH 10.0. The GS release was considerably slow with an initial burst of about 25% within 24 h and reached 35% in 10 days. On the other hand, the Nap release was much faster with approximately 62% cumulative release within 24 h and 75% in 10 days.

The release behavior was further studied by changing pH value of the release medium. Fig. 5A shows the drug release from DDDS at pH 1.2 for 2 h followed by the release at pH 10.0. After releasing in the medium at pH 1.2 for 2 h, the GS was completely released, while only about 17% of the Nap was released. The release medium was then adjusted from pH 1.2 to pH 10.0. Due to the increase of the pH, the release of Nap dramatically increased. More than 55% was released within 2 days, and the amount of Nap released reached 72% after 10 days. This result demonstrated that GS and Nap loaded in DDDS can be selectively released by controlling the pH of the medium. After GS was totally released in pH 1.2, Nap was then released at pH 10.0. On the contrary, as shown in Fig. 5B, if the DDDS was first put in the medium at pH 10.0, a fast release of Nap was observed. After 24 h, the cumulative Nap release was about 65%, while the GS release was only about 26%. When the pH value of the release medium was changed to 1.2, the release rate of GS sharply increased with 100% cumulative release within 1 h.

Table 1
The drug loading before and after compounding

	GS loading ($mg_{(GS)}/g_{(MBG)}$)	Nap loading ($mg_{(Nap)}/g_{(PBLG\text{-}g\text{-}PEG)}$)
MBG/GS	405	–
PBLG-g-PEG/NAP	–	86
Composite DDS	321	76

4. Discussion

Fig. 6 schematically illustrates the drug loaded mesoporous bioactive glass/PBLG-g-PEG nanomicelle composites. The spherical nanomicelles were adsorbed onto the surface of MBG through hydrogen bond, and the morphology of the micelles was reserved. In this dual-drug loaded system, gentamicin sulfate (GS) and naproxen (Nap) were hosted in the mesopores of the bioactive glass and the core of the core-shell type polypeptide nanoparticles, respectively.

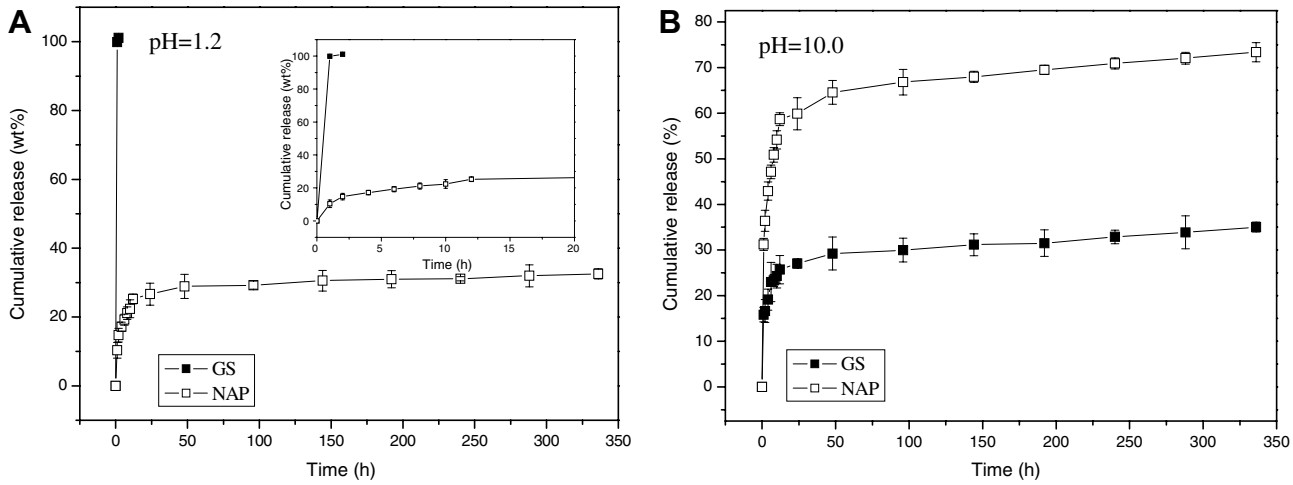

Fig. 4. Cumulative release of GS and Nap from the dual-drug delivery system at different pH and 37 °C.

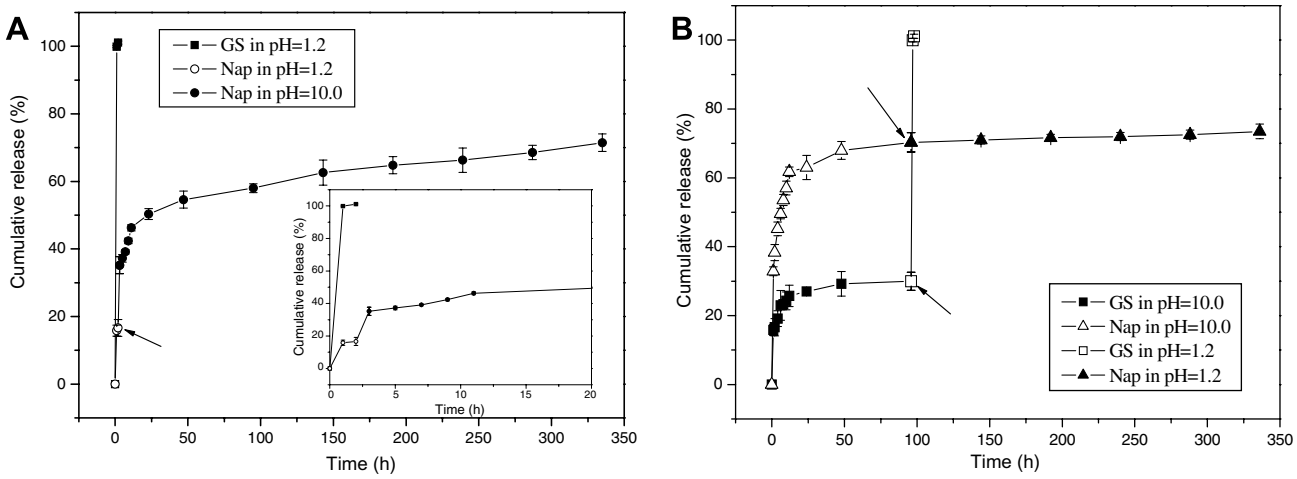

Fig. 5. Cumulative releases of drugs from the dual-drug delivery system with changing pH value of release medium. (A) The arrows indicate the points at which hydrochloric acid buffer (pH 1.2) was changed with carbonate–bicarbonate buffer (pH 10.0). (B) The arrows indicate the points at which carbonate–bicarbonate buffer (pH 10.0) was changed with hydrochloric acid buffer (pH 1.2).

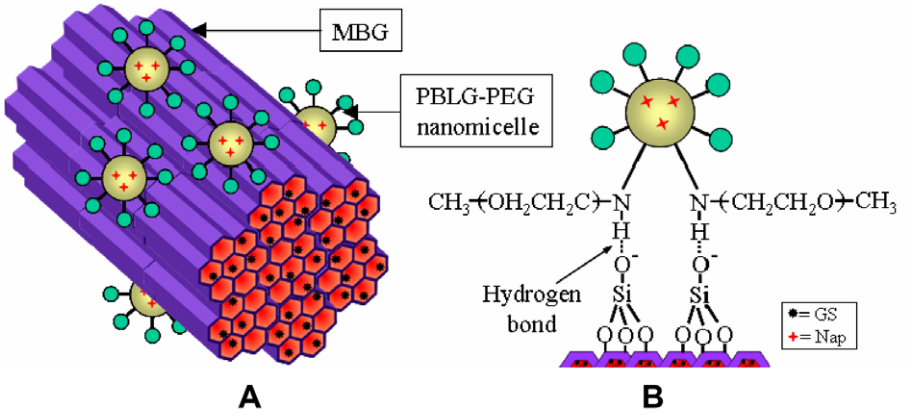

Fig. 6. (A) The scheme of the dual-drug delivery system based on mesoporous bioactive glass/PBLG-g-PEG nanomicelle composite. (B) The scheme of interaction between MBG and polypeptide nanomicelles.

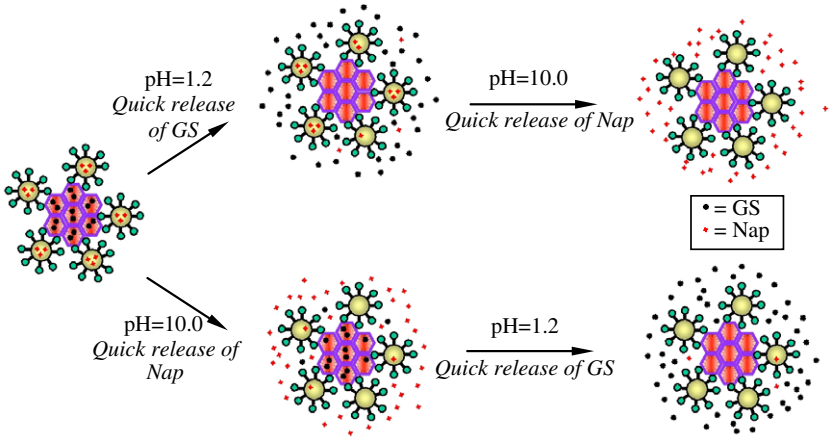

Fig. 7. Schematic illustration of the dual-drug delivery system, which demonstrated a pH-responsive drug release behavior.

Fig. 7 schematically illustrates the MBG/nanomicelle composite release system, which was designed to demonstrate pH-controlled dual-drug release. During the release process, the GS and Nap diffused through the mesopores of MBG and PBLG-g-PEG shells into the release medium, respectively. The release of the two drugs was controlled by

adjusting the pH of the medium and GS was released from MBG at acidic medium [21], while Nap was released from nanomicelles at basic medium [24].

This difference in release behavior can be mainly attributed to the different release rate of GS from MBG and Nap from PBLG-g-PEG at different pH values. In general, hydrophilic drugs encapsulated in traditional drug delivery systems are controlled by the diffusing mechanism [25,26]. In our composite delivery system, the rate of GS release from MBG was controlled not only by the diffusion mechanism, but also by the desorption rate of GS from the pore surface where the Si–OH groups of the MBG interacted with GS [21]. The GS-MBG interaction can be illustrated as: $Si–O–H + GS \leftrightarrows Si–O\cdots GS + H^+$. When the pH value of the release medium decreased, the GS desorption rate rapidly increased and led to a quick release of GS. With the decrease of H^+ concentration, GS molecules become difficult to be desorbed from MBG surface, which resulted in the slow release rate. In contrast, a hydrophobic drug has limited water-solubility. Using amphiphilic polymeric core-shell nanoparticles, sustained and controlled drug release can be achieved. At acidic pH, Nap entrapped in the cores of nanomicelles was minimally ionized, which led to a slow release. With the increase of pH value, carboxyl groups of Nap were gradually ionized, and the Nap molecules in the PBGL-g-PEG core-shell nanomicelles were ionized and migrated more easily from the inner core to the outer surface [24]. Therefore, Nap release rate increased with the increase of ionization. The release profiles of naproxen and gentamicin from the dual-drug delivery system suggested that two different drugs could be controlled released by changing the pH value of the environment.

5. Conclusions

In summary, we demonstrate for the first time, a novel dual-drug delivery system based on mesoporous bioactive glass/PBLG-g-PEG nanomicelle composites. In this composite system, hydrophilic gentamicin was loaded within the mesopores of the bioactive glasses and hydrophobic naproxen was encapsulated in the core of the polypeptide nanomicelles. The polypeptide nanomicelles were adsorbed on the surface of the mesoporous bioactive glasses through hydrogen bonds and the release of each individual drug was controlled by the pH of the surrounding environment. The hydrophilic gentamicin was quickly released from mesopores of MBG in acidic medium, while the hydrophobic naproxen was quickly released from the polypeptide nanomicelles in basic medium. With the system presented here, multi-drug delivery can be achieved in a controlled manner.

Acknowledgments

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