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Organic–inorganic hybrid anion exchange hollow fiber membranes: A novel device for drug delivery

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ABSTRACT

The clinical use of nonsteroidal anti-inflammatory drugs (NSAIDs) (such as sodium salicylate (NaSA)) for the treatment of chronic arthritis is limited due to the adverse effects and patient non-compliance. In order to solve these problems, anion exchange hollow fiber membranes (AEHFMs) are proposed for the first time here as potential drug carriers. Brominated poly(2,6-dimethyl-1,4-phenylene oxide) (BPPO) is used as the starting membrane material. In-situ sol–gel process of γ-methacryloxypropyl trimethoxysilane (γ-MPS) in BPPO matrix is operated so as to enhance the membranes' thermal and dimensional stability. The performances of the membranes in controlled release of the drug (NaSA as the model drug) are improved accordingly. Loading and release experiments illustrate that the hybrid AEHFM can bind salicylate (SA^-) at a high loading efficiency (28.4%), and the retention of the drug on the membrane matrix is significantly prolonged (drug released in 7 days under physiological condition: 51.9%, neglecting the drug bound by protein). Meanwhile, the membrane is biocompatible and can support the adherence, growth, and survival of human cells. Overall, the prepared AEHFM is a promising scaffolding material for drug delivery and tissue engineering.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used drugs, primarily for symptoms associated with osteoarthritis and other chronic musculoskeletal conditions (Chi and Jun, 1990; Marie, 1998). However, the adverse effects caused by oral administration have limited their clinical applications (Marie, 1996), including gastrointestinal side effects (such as dyspepsia, gastrointestinal bleeding, and even perforation) (Denis, 1999; Gabriel et al., 1991), renal side effects, and some additional side effects (such as hypersensitivity reactions and distinct salicylate intoxication) (Marie, 1996). Patient non-compliance is also a common therapeutic problem for systemic or intra-articular injection as well as oral administration (Jacobs et al., 1988), because most NSAIDs have short plasma elimination half-life (2–4 h) and must be administered in multiple daily doses to maintain therapeutic blood levels.

Controlled release is an alternative way to overcome these problems, since it can provide a relatively steady release rate, optimize the drug therapeutics and improve patient compliance. For developing an ideal controlled drug release system, researches have been mainly focused on the *in vitro* and *in vivo* release rate, pharmacodynamic and pharmacokinetic behaviors of a drug (Guo et al., 2009). The release behavior of a certain drug depends much on the physicochemical parameters of the delivery vehicle, which determines the interaction pattern and strength between the drug and the carrier. Electrostatic interactions (pure ion-exchange mechanism) and non-electrostatic interactions (hydrophobic interactions and/or hydrogen bonding) have been proposed to be the major interaction patterns (Hanninen et al., 2005).

Ion exchange materials, including resins, gels, fibers, and membranes, have been attractive candidates of ionic drugs carriers, due to their advantageous properties such as the relatively high capacity of drug loading, the easily executed loading procedure, good

Abbreviations: AEHFM, anion exchange hollow fiber membrane; BPPO, brominated poly(2,6-dimethyl-1,4-phenylene oxide); BPPO(+), AEHFM without hybridization based on BPPO; BPPO(+)-SA^-, the BPPO(+) HFMs loaded with NaSA; BPPO-SA^-, the BPPO HFMs loaded with NaSA; BPPO-γ-MPS(+), AEHFM hybridized with γ-MPS based on BPPO; BPPO-γ-MPS(+)-SA^-, the BPPO-γ-MPS(+) HFMs loaded with NaSA; BSA, bovine serum albumin; DCR, dimensional change ratio (in water), %; DMSO, dimethyl sulfoxide; Glc, glucose; HFM, hollow fiber membrane; IEC, ion exchange content, mmol/g dry membrane; IEHFM, ion exchange hollow fiber membrane; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; MWCO, molecular weight cut off; NaSA, sodium salicylate; NSAID, nonsteroidal anti-inflammatory drug; PBS, phosphate buffer solution, confected with Na_2HPO_4–KH_2PO_4; SA^-, salicylate; SEM, scanning electron microscope; TEA, triethylamine; TEOS, tetraethoxysilane; γ-MPS, γ-methacryloxypropyl trimethoxysilane.

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Nomenclature

A	membrane surface area, cm^2
c	the concentration of drug in the test tube after drug loading, mg/mL
c_0	the concentration of drug in the test tube before drug loading, mg/mL
D	Diffusion coefficient, cm^2/s
K	Langmuir equilibrium constant, mL/mg
q	adsorption amount of drug, mg/g dry membrane
Q	amount of drug released, mg
q_m	maximum amount of drug adsorption as c_0 increases, mg/g dry membrane
S	total content of drug absorbed by the HFM, mg/g dry membrane
t	time, s
Td	temperature at 5% weight loss, °C
W_R	water content, %

drug-retaining properties, and uniform drug release (Hanninen et al., 2005; Jiang et al., 2006; Raghunathan et al., 1981; Zhang et al., 2006). Among different ion exchange materials, ion exchange resins were first proposed for controlled release before more than 50 years. And the principles, selection and application results of resins for controlled drug release have been systematically elaborated (Guo et al., 2009). However, the controlled release performances require further improvement; especially the release rate needs to be decreased. Accordingly, ion exchange resins were surface-coated by polymeric films, such as semi-permeable membranes (Halder and Sa, 2006; Raghunathan et al., 1981) or encapsulated by hollow fibers (Hussain et al., 1989a). And then, the release rate can be effectively decreased. Intrigued by the improvement, some other researchers have tried ion exchange fibers and membranes directly for drug controlled release. High drug loading capacity and strong ability to maintain constancy in the drug delivery profiles have been achieved (Hanninen et al., 2005; Sundell and Stenlund, 2001).

To date, the researches of ion exchange membranes for controlled drug release have mainly involved flat membranes. Ion exchange membranes of another physical shape, namely, hollow fiber membranes (HFMs), show distinguished characterizations of self-supporting, convenience for assembling, low cost, large effective mass transfer area and high flux (Abetz et al., 2006). The application of ion exchange hollow fiber membranes (IEHFMs) in biomedical fields such as protein separation and purification (Hagiwara et al., 2005; Kubota et al., 1997), enzymes immobilization (Ye et al., 2005), bioreactors (De Bartolo et al., 2009; Ye et al., 2006) and artificial organs (Unger et al., 2005; Yang and Lin, 2001) have been reported with noticeable effectiveness. Nevertheless, the reports of IEHFMs for the application of drug delivery are much less. Only few papers were reported in the field involving cation exchange HFMs for the controlled release of dopamine, propranolol, etc. (Hussain et al., 1989b; Jenke, 1989). Studies on significant aspects such as the biocompatibility of the membrane materials have not been reported. Therefore, further and more systematic development of drug delivery system with IEHFMs would be meaningful.

In this paper, IEHFMs are first proposed to upload and retard the release of ionic drugs. Two main objectives were to be pursued: one was to prolong the retention of the drug and the other was to achieve high biocompatibility of the membranes. In order to attain the above goals, brominated poly(2,6-dimethyl-1,4-phenylene oxide) (BPPO) was chosen as the base HFMs, since it is chemically stable, non-degradable and easy to be charged.

For improving the swelling resistance of the membranes and thereby the drug release performances, in situ sol–gel process is conducted to form organic–inorganic matrix. Previous researches have demonstrated that the incorporation of the inorganic component by small molecule silanes (such as tetraethoxysilane (TEOS)) has no negative influence on the biocompatibility of the biomaterials but can control the pore size and the hydrophilicity of the materials (Kim et al., 2010). In our earlier study, the modification results of BPPO membranes by different organic silanes have also been evaluated with respect to hydrophilicity, dimensional stability and protein adsorption, etc. (Wang et al., 2010). The membranes from γ-methacryloxypropyl trimethoxysilane (γ-MPS) showed proper ion exchange capacity and water content (Wang et al., 2010). Besides, the ester group of γ-MPS is theoretically non-toxic, which is beneficial for the biocompatibility of the membrane. Therefore, γ-MPS is chosen in this work for preparation of BPPO-based hybrid AEHFMs. The membrane properties related with the controlled drug release is investigated. Sodium salicylate (NaSA), a well-established NSAID in clinical trails which has anti-inflammatory effect for chronic arthritis, is studied as the model drug. The focus of this work is to determine whether and how the modified AEHFMs can load and retard the release of NSAIDs, and serve as a biocompatible drug carrier.

2. Materials and methods

2.1. Materials

Brominated poly(2,6-dimethyl-1,4-phenylene oxide) (BPPO) HFMs were kindly supplied by Tianwei Membrane Corporation Ltd. of Shandong (China) with 53% benzyl substitution ratio and 47% aryl substitution ratio. γ-methacryloxypropyl trimethoxysilane (γ-MPS) was purchased from Shanghai Yaohua Chemical Plant (Shanghai, China). Triethylamine (TEA), bovine serum albumin (BSA), glucose (Glc) and ethanol were purchased from Sinopharm Chemical Reagtent Co., Ltd. (Shanghai, China). Sodium salicylate (NaSA) was obtained from Tianjin Damao Chemical Reagent Factory (Tianjin, China). Dialysis membrane (molecular weight cut off, MWCO ~ 3500 Da), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay kit, and dimethyl sulfoxide (DMSO) were obtained from BBI Inc. (Shanghai, China). The HeLa cells were purchased from Keygen Co. (Nanjing, China). γ-MPS and TEA were diluted with ethanol to 1.0 mol/L before use. Double-distilled water was used throughout.

2.2. Preparation and characterizations of hybrid AEHFMs

The hybrid AEHFMs were prepared through modification of the BPPO base HFMs by three steps: pretreatment, sol–gel process and quaternization (Fig. 1a). The procedures have been described in details previously (Wang et al., 2010) and would be summarized here as following.

(1) The pretreatment step: The BPPO HFMs were immersed in 1.0 mol/L KOH aqueous solution at 60 °C for 24 h and then dried at 45 °C for 6 h. (2) The sol–gel process: The pretreated membranes were kept for 12 h in γ-MPS/ethanol solution at room temperature. Afterwards, 0.02 mol/L HCl aqueous solution was added. The molar ratio of Si, HCl and H_2O (from HCl aqueous solution) was $1:2.16\times10^{-3}:6$. After 3 h, the membranes were taken out, washed and dried at 45 °C for 6 h. (3) The quaternization step: The membranes were kept in TEA/ethanol solution for 6 h at room temperature, then washed, air-dried for 12 h, and heated at 45 °C for 6 h. The membranes obtained were denoted as BPPO-γ-MPS(+).

For comparison, another type of HFMs were prepared without the sol–gel process (step 2) and denoted as BPPO(+) (Fig. 1b).

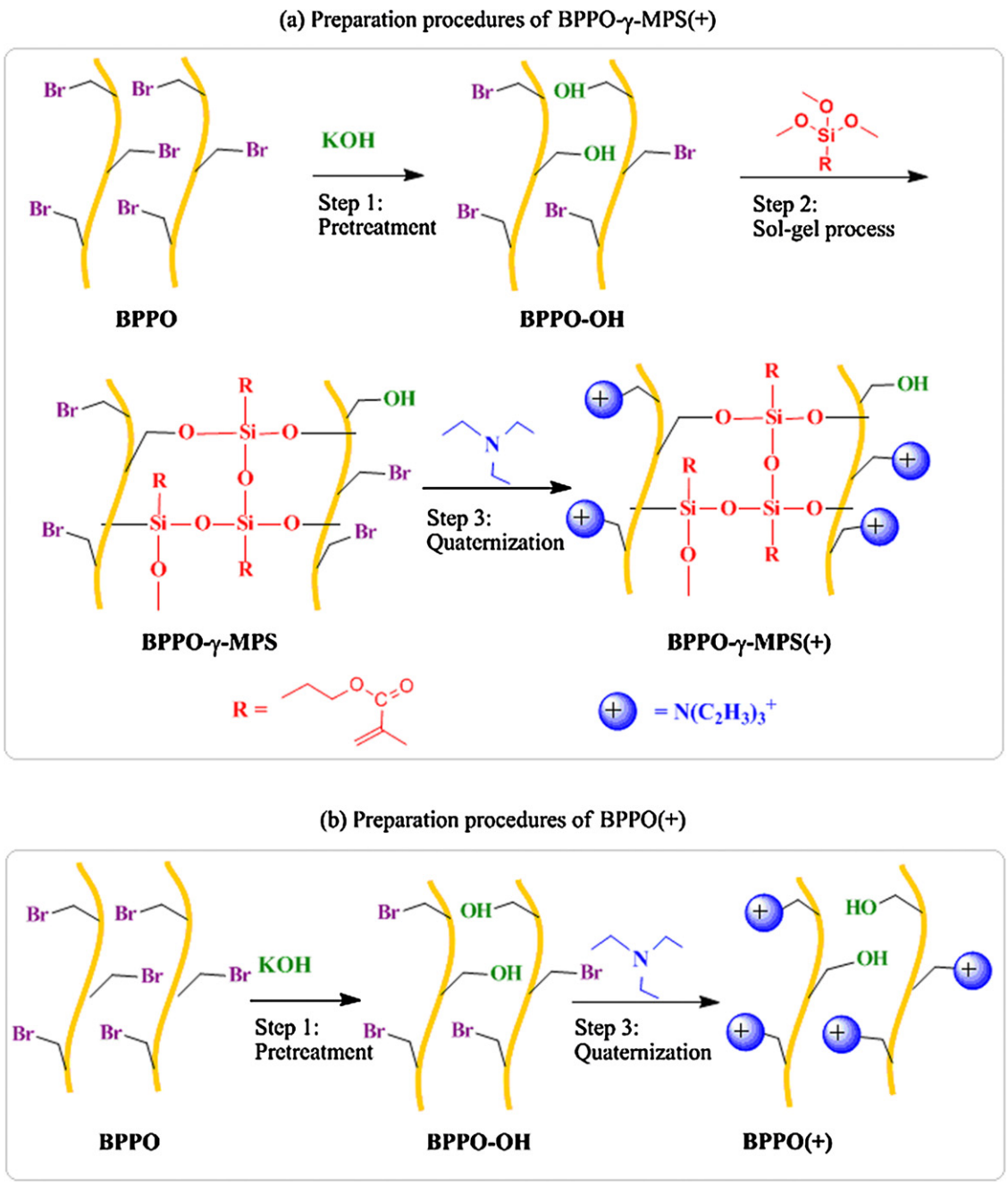

Fig. 1. The preparation procedures of (a) BPPO-γ-MPS(+) and (b) BPPO(+) HFMs from BPPO base membrane.

Characterizations concerning the membranes morphology, charged property, hydrophilicity, dimensional stability and thermal stability were illustrated in our previous work (Wang et al., 2010) and summarized here in Table 1.

2.3. Drug loading studies

The HFMs of BPPO, BPPO(+) and BPPO-γ-MPS(+) were loaded with NaSA through static adsorption. Dry membranes (0.05 g) were added into NaSA aqueous solutions (4 mL) and kept at 30 °C for 48 h. Then the membranes were taken out and washed by water (with a total volume of 5 mL) for several times to ensure that the drug adhered on the surface of the membranes was removed. For convenience of later discussion, the HFMs loaded with salicylate (SA^-) were denoted as BPPO-SA^-, BPPO(+)-SA^- and BPPO-γ-MPS(+)-SA^- respectively. The washing solutions and the adsorption solution after drug loading were collected for concentration analysis.

For the BPPO-γ-MPS(+) HFMs, the time of adsorbing equilibrium was determined by on-line measurement for 48 h. Meanwhile, the effect of original drug concentration (NaSA concentration from 0.01 to 20 mg/mL) and ion strength (10 mg/mL NaSA with extra NaCl concentrations of 0, 0.1, 0.2, 0.3, 0.4, 0.5 mol/L) were studied for 24 h.

During the above measurements, the concentrations of SA^- were determined from the absorbance at 295 nm using a PGENERAL (UT-1901) UV–vis spectrophotometer (Beijing, China). And all the solutions before UV test were diluted into a concentration of 1–30 mg/L to ensure the concentration in the linear range of the

Table 1
Properties of BPPO(+) and BPPO-γ-MPS(+) HFMs.

Hollow fiber membrane	BPPO(+)	BPPO-γ-MPS(+)
Size (mm)	Inner diameter: 0.71 Outer diameter: 1.11 Length: 65	Inner diameter: 0.70 Outer diameter: 1.06 Length: 65
Functional group	Quaternary ammonium groups	Quaternary ammonium groups
Ion exchange capacity (IEC) (mmol/g dry membrane)	1.87	1.76
Water content (W_R) (%)	97.0	62.9
Dimensional change ratio (DCR) (in water) (%)	34.2	12.9
Thermal degradation temperature (Td, temperature at 5% weight loss) (°C)	179.4	181.2

UV test. The drug loading content was calculated by the following equation:

$$S = \frac{4(c_0 - c)}{0.05} \quad (1)$$

where S (mg/g dry membrane) is the total content of SA^- absorbed by the HFM; c_0 and c is the concentration of SA^- in the test tube before and after drug loading.

The loading efficiency versus original drug concentration curves of SA^- were fitted by the Langmuir isotherm mechanism:

$$q = \frac{q_m K c_0}{1 + K c_0} \quad (2)$$

where K is Langmuir equilibrium constant (mL/mg). q is the adsorption of SA^- and q_m is the maximum amount of drug adsorption. By curve fitting of the drug loading data under different drug concentrations, the value of q_m and K can be calculated.

2.4. Release behaviors

The effects of external phase conditions on the release behaviors of BPPO-γ-MPS(+)-SA^- were studied, as detailed in the following: BPPO-γ-MPS(+)-SA^- from loading with 10 mg/mL NaSA was immersed into a constant volume (50 mL) of aqueous mediums with different pH values (5.0, 7.4 and 9.0), different ion concentrations (0, 0.2 and 2.0 mol/L NaCl without pH adjusting), different concentrations of protein (0, 70 and 140 mg/mL bovine serum albumin (BSA)) and sugar (0, 100 and 200 mg/dL glucose). The releasing systems were kept in water bath at 37 °C for 12 h and sampled (3 mL) at each predetermined sampling time. Fresh medium was added immediately after each sampling. The accumulative amount of SA^- released from BPPO-γ-MPS(+)-SA^- was determined by the UV absorbance at 295 nm.

Furthermore, a long-period releasing experiment in a simulated body fluid medium (0.2 mol/L PBS, 100 mg/dL glucose and 70 mg/mL BSA, pH 7.4) was performed for one week.

During the above releasing experiments, pH values of 5.0, 7.4 and 9.0 were obtained from buffers of Na_2HPO_4–citric acid, Na_2HPO_4–KH_2PO_4 and borax–NaOH respectively. The concentration of the buffers was kept constant (0.02 mol/L) to maintain the same ionic strength. Besides, dialysis bag was used when BSA was present: BPPO-γ-MPS(+)-SA^- was added into a dialysis bag (MWCO ~ 3500 Da) containing BSA solution (5 mL). Then the dialysis bag was immediately immersed into the buffer solution without BSA (45 mL). One control experiment was performed to find out the binding of protein (BSA) with NaSA: 15 mg NaSA was added into the dialysis bag containing 5 mL BSA solution (70 mg/mL or 140 mg/mL). Then the dialysis bag was immersed into pure water (45 mL). The concentration of NaSA out of the dialysis bag was measured at intervals until it reached a constant level.

In order to study the effect of membrane structure on the drug release behavior, the releasing behavior of BPPO(+)-SA^- in pure water was observed for 12 h. That was, no buffer, BSA or sugar was used. The data were taken for comparison with BPPO-γ-MPS(+)-SA^-.

In order to study the effect of drug loading on drug release behavior, the drug release of BPPO-γ-MPS(+)-SA^- loaded with 2 mg/mL, 5 mg/mL and 10 mg/mL NaSA was investigated in 0.2 mol/L NaCl solution for 12 h.

Diffusion coefficients D can be obtained through fitting the release curves by the Higuchi equation (Higuchi, 1962):

$$\frac{Q}{A} = 2c_0\sqrt{\frac{Dt}{\pi}} \quad (3)$$

where Q/A is the amount of drug released per unit area at the time t, and c_0 is the initial concentration of SA^- in BPPO-γ-MPS(+)-SA^- or BPPO(+)-SA^-. A is the membrane surface area and can be calculated from the inner, outer diameter and the length of the membrane. Higuchi equation has been mainly used to represent the release from a slab. Nevertheless, previous researches have also utilized it for macroscopical cylinders (Zhang et al., 1994).

2.5. Biocompatibility evaluation

The biocompatibility of the BPPO-γ-MPS(+) hollow fiber membrane was evaluated to ensure that it has the potential to be implanted into human body. The membrane samples were washed by ethanol and water in turn for 10 times. Afterwards they were dried and cut into short sections (length around 3 mm, average weight 2.983 mg per section). For thorough sterilization, the membrane sections were transported into super clean bench and washed by ethanol for more than 20 times, then by double-distilled water for more than 20 times. The subsequent biocompatibility experiments included the following two parts:

(1) Growth of human cells on the AEHFMs: HeLa cell, one kind of adherent cell, was chosen as the model cell. First, cells were grown continuously as a monolayer at 37 °C, and 5% CO_2 in the cell culture medium, which consisted of Dulbecoo's modified Eagle's medium (DMEM), streptomycin (100 μg/mL), penicillin sulphate (100 units/mL) and 10% heat-inactivated fetal calf serum (FCS). The membrane sections were washed by the cell culture medium, and then added into the wells of 24 well plates (2 membrane sections per well). A total of 3 wells were used for parallel test. Then about 5×10^4 cells/well were seeded in the plate. The growth state of the cells was investigated by an Axiovert 200 fluorescence microscope (Carl (ZEISS) Shanghai Co., Ltd., China) after 48 h and 72 h, respectively. Membrane sections without cells were handled in an identical manner and used as a negative control.
(2) Cytotoxicity studies of the membranes: About 1×10^5 cells/well were seeded in 24 well plate. After 24 h, the membrane sections were put into the wells (0, 1, 2, 4, 8 or 16 membrane sections per well). The plate was maintained at 37 °C, and 5% CO_2 for 24 h, and then the membrane sections were carefully removed. Subsequently, another 1 mL cell culture medium and 100 μL MTT/PBS solution was added into each well in sequence. After 4 h of incubation at 37 °C and 5% CO_2, the medium in each well was removed and replaced by 700 μL DMSO. The plate was shaken for 10 min at 1000 rpm and at last read by ELX 800 enzyme microplate reader (BIO-TEK, USA) at 490 nm.

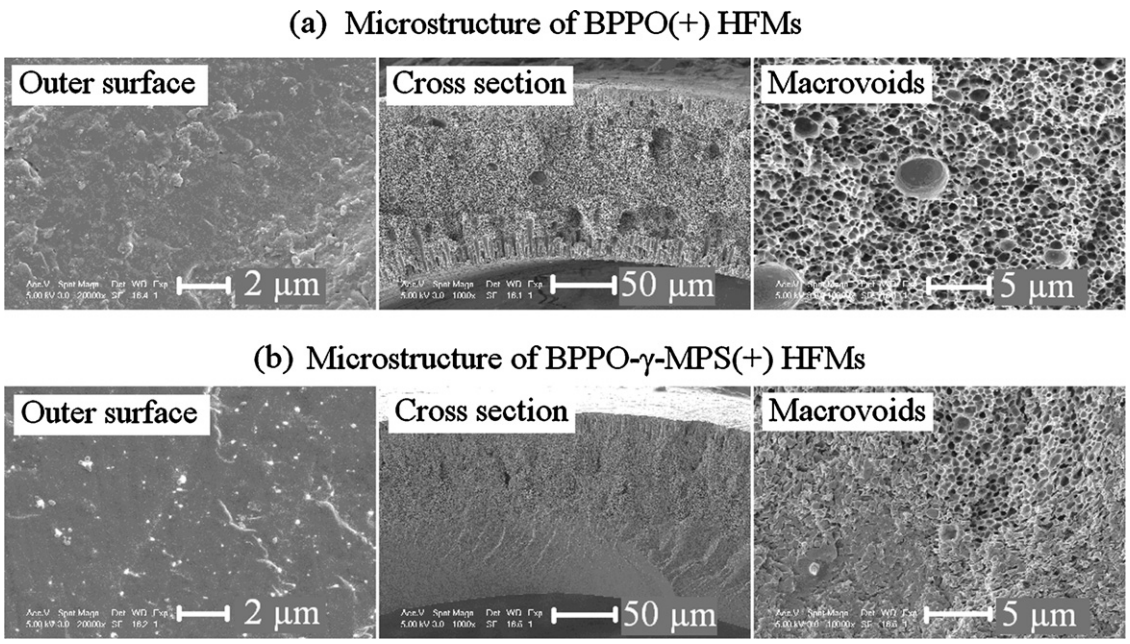

Fig. 2. SEM micrographs of the BPPO(+) and BPPO-γ-MPS(+) HFMs, including the outer surface, cross sections and macrovoids.

3. Results and discussion

3.1. Characterizations of the AEHFMs

The AEHFM of BPPO-γ-MPS(+) has been obtained from hybridization by γ-MPS. During the in situ sol–gel process of γ-MPS, inorganic silica component is incorporated and partially crosslinked with BPPO matrix through Si–O–C bonding. Compared with BPPO(+) membrane without hybridization, BPPO-γ-MPS(+) membrane displays improved properties in respect of dimensional stability and thermal stability, which may significantly affect the drug loading and release behavior of the membrane and hence will be summarized here (Table 1):

(1) Dimensional stability of the HFMs is indicated by the dimensional change ratio (DCR), which is determined by the following equation:

$$\text{DCR}\ (\%) = \frac{L_2 - L_1}{L_1} \times 100\% \quad (4)$$

where L_1 and L_2 are the length of the HFMs in dry and wet state, respectively. The DCR value of BPPO-γ-MPS(+) is 12.9%, much lower than that of BPPO(+) (34.2%). Visual inspection shows that BPPO(+) tends to be softer and more distorted when immersed in water for a period of time (≥30 min). BPPO-γ-MPS(+) can generally remain the original shape.

(2) The water content (W_R) of the membrane is decreased from 97.0% to 62.9%.

(3) Thermal stability is slightly improved and Td value is increased from 179.4 °C to 181.2 °C.

According to previous reports (Guo et al., 2009), the improvement of dimensional stability and the decrease of water content are advantageous for slow or gradual release of the drugs, because the membrane swelling is suppressed and the drug release can be retarded better. Our previous study of BPPO flat membrane also proves that the change of the swelling behavior and water content can be used to control the permeability of salicylate (Zhang et al., 2006). Another potential benefit by the improvement of the dimensional stability is that the side effects caused by deformation may be decreased when the membrane is applied in implanted drug carrier or tissue engineering.

Besides the properties as summarized in Table 1, the microstructures of the membranes are also important to their drug release performances. Hence BPPO(+) and BPPO-γ-MPS(+) membranes have been freshly fractured and observed by SEM in this work. Fig. 2 demonstrates that the surface of BPPO-γ-MPS(+) HFM is relatively smoother than that of BPPO(+), and the macrovoids in cross section are smaller. These observations confirm further that silica component is incorporated and the membrane crosslinking is improved after hybridization by γ-MPS.

3.2. Drug loading efficiency of the HFMs

The drug loading efficiency of BPPO(+) and BPPO-γ-MPS(+) HFMs were preliminarily studied. BPPO base membrane was also investigated for comparison. Results show that, after immersed in 10 mg/mL NaSA for 48 h, BPPO only has a drug loading efficiency of 1.84% (18.7 mg/g dry membrane), while BPPO(+) and BPPO-γ-MPS(+) display 22.41% and 20.89% (288.9 and 264.1 mg/g dry membrane) respectively (Fig. 3). This observation indicates that (1) SA^- is adsorbed onto the membranes mainly through electrostatic interactions; and (2) the drug loading efficiency of the membrane is well retained after hybridization by γ-MPS, because the ion exchange content (IEC) remains high (1.76 mmol/g, shown in Table 1).

The loading efficiency of BPPO-γ-MPS(+) during 48 h was further investigated to determine the drug adsorption dynamics. Fig. 4a shows that the loading rate is high during the first 8 h (87% at 8 h and 95% at 24 h). The adsorption equilibrium time is around 36 h. Therefore, the loading period has been chosen as 24 h for later loading and release experiments. The loading concentration dependent and ion strength dependent data in Fig. 4b show that the loading efficiency of SA^- increases with initial drug concentration, which is in accordance with the results in the literature (Boudy et al., 2002). Through curve fitting by Langmuir isotherm mechanism (Eq. (2)), the value of q_m is calculated to be 396.9 ± 7.2 mg/g (2.48 ± 0.04 mmol/g), and K is 0.32 ± 0.02 mL/mg. The q_m value is relatively high as compared with some reported values. For example, our previous flat membrane based on BPPO exhibits an extremely low SA^- load-

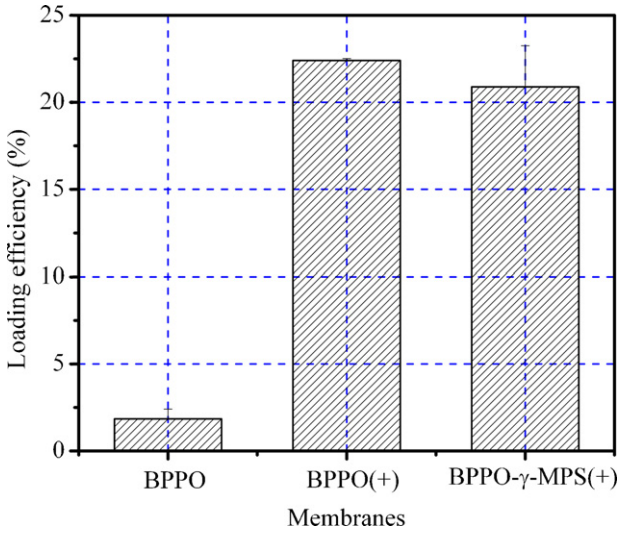

Fig. 3. The loading efficiency of BPPO, BPPO(+) and BPPO-γ-MPS(+) HFMs after immersed in 10 mg/mL sodium salicylate for 24 h.

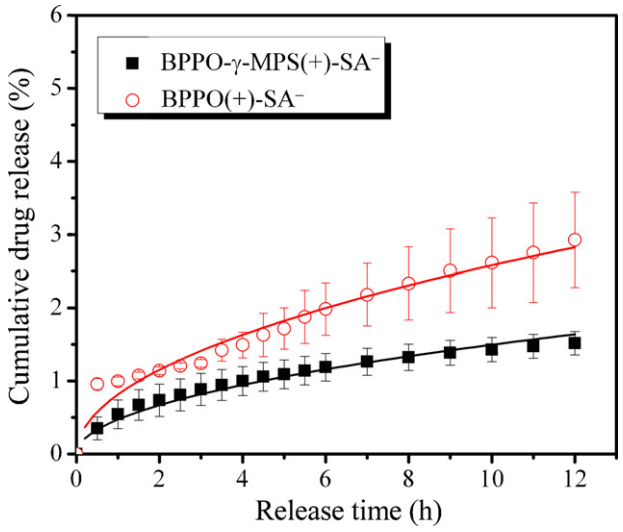

Fig. 5. Release behaviors of salicylate (SA^-) from BPPO(+)-SA^- and BPPO-γ-MPS(+)-SA^- complexes in pure water at 37 °C.

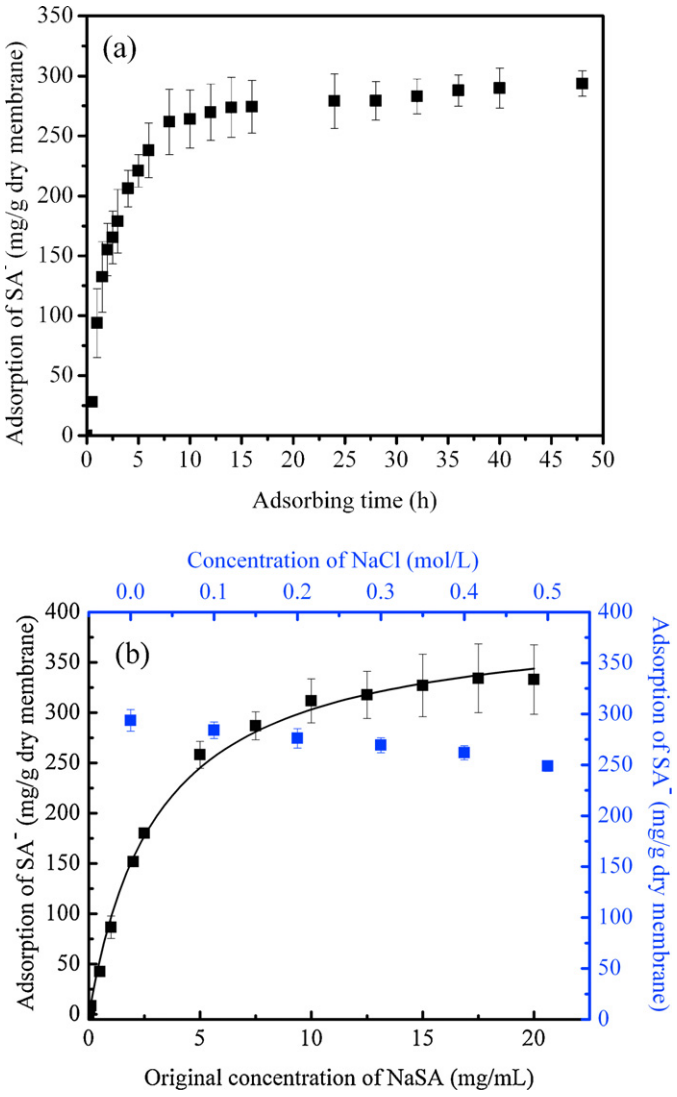

Fig. 4. The loading of salicylate (SA^-) by BPPO-γ-MPS(+) HFM at 30 °C, without pH justing. (a) Adsorbing time curve; the original NaSA concentration was 10 mg/mL; (b) Original drug concentration dependent and ion concentration dependent; the original concentration of NaSA was 10 mg/mL when the adsorption-NaCl concentration curve was observed.

ing content of 0.016 mmol/g (Zhang et al., 2006). A metal-chelate embedded polymer can load copper salicylate with an efficiency of 0.267 mmol/g (Sumi et al., 2008). The loading contents of SA^- onto anion exchange fibers of Smopex®-103pe, Smopex DS-218v and Smopex®-108 are 1.4–1.9 mmol/g (Hanninen et al., 2005; Jaskari et al., 2000). The outstanding drug loading capability of BPPO-γ-MPS(+) is due to both the highly microsporous structure and the relatively high IEC.

Fig. 4b also illustrates the ionic strength dependence of drug loading efficiency. When the concentration of NaCl increases from 0 to 0.5 mol/L, the loaded SA^- reduces from 293.7 to 248.9 mg/g dry membrane. This result is in accordance with earlier studies of Okada et al. (Okada et al., 1987) and can be explained as following: there are mainly three types of interactions between the drugs and the polymer drug carriers that affect the drug loading efficiency and the release rate: (1) electrostatic interaction; (2) hydrogen bonding; and (3) hydrophobic interaction (Jiang et al., 2006). Increase of ionic strength can inhibit electrostatic binding of polymer drug carriers with oppositely charged drugs (Okada et al., 1987) and hence the drug loading is decreased. Besides, the saturation adsorption of the drug on per unit of membrane mass (q_m = 2.48 mmol/g) is 1.4 times as large as the density of the charged groups (IEC = 1.76 mmol/g) of BPPO-γ-MPS(+), indicating that non-electrostatic forces between the membrane and the drug are also involved. Hydrogen bonding can be formed between the oxygen atoms of BPPO-γ-MPS(+) (from ester groups, –SiOH or –Si–O–Si– groups) and –OH groups of the drugs. Hydrophilic interactions may exist between drugs and the benzene rings or methylvinyl groups of BPPO-γ-MPS(+).

3.3. Release behaviors of the AEHFMs

3.3.1. Release behaviors of BPPO(+)-SA^- and BPPO-γ-MPS(+)-SA^- in pure water

The release behavior of BPPO-γ-MPS(+)-SA^- in pure water was examined and the result is shown in Fig. 5. BPPO(+)-SA^- was also investigated for comparison because of its high drug loading efficiency. Fig. 5 shows that only 2.93% and 1.52%, that is, 8.5 mg/g and 4.0 mg/g dry membrane of the entrapped drugs are released from BPPO(+)-SA^- and BPPO-γ-MPS(+)-SA^- in pure water during the period of 12 h, respectively. Therefore, both BPPO(+)-SA^- and BPPO-γ-MPS(+)-SA^- are able to effectively retard the release of the drug. The SA^- diffusion coefficients (D) for BPPO(+)-SA^- and BPPO-γ-MPS(+)-SA^- are 1.56×10^{-2} cm^2/s and 5.24×10^{-3} cm^2/s

according to Higuchi equation (Eq. (3)). These values are much lower than some reported values. For example, the effective diffusion coefficient of SA^- in water from polycaprolactone (PC) is 5.67×10^{-5} cm^2/h (0.20 cm^2/s) (Sprockel et al., 1997).

Comparison between BPPO(+)-SA^- and BPPO-γ-MPS(+)-SA^- shows that the release of SA^- from BPPO-γ-MPS(+)-SA^- is obviously slower. That means the hybridization by γ-MPS is advantageous for the retarding of drug release. As discussed in Section 3.1, the inorganic silica network in BPPO-γ-MPS(+) makes the membrane structure more compact and increases the swelling resistance. Hence the affinity of drugs to the membrane is enhanced. Comparatively, BPPO(+) with higher swelling degree and more distorted structure is easier to let loose the entrapped drugs. Thus, the hybridization by γ-MPS is very meaningful to obtain a potential drug carrier with outstanding ability for controlled drug release.

3.3.2. Release behaviors of BPPO-γ-MPS(+)-SA^- in different external phase condition

In order to fully determine the ability of the BPPO-γ-MPS(+) HFM of retarding the SA^- release, we have investigated the *in vitro* release of SA^- at different pH conditions, ion concentrations, BSA concentrations, glucose concentrations as well as in a simulated body fluid. The result curves, as shown in Fig. 6, are fitted by Higuchi equation (Eq. (3)), and the diffusion coefficients (D) are listed in Table 2. The main findings and conclusions will be elaborated in the following.

Table 2
Diffusion coefficients (D) of salicylate (SA^-) from BPPO-γ-MPS(+)-SA^- at 37 °C under different external phase conditions.

External phase conditions	D (cm^2/s)	D/D_0*
Double-distilled water (D_0)	5.24×10^{-3}	1
0.2 mol/L NaCl	1.04	199
2.0 mol/L NaCl	4.78	911
pH 5.0	7.88×10^{-1}	150
pH 7.4	4.46×10^{-1}	85.1
pH 9.0	1.42×10^{-1}	27.0
70 mg/mL BSA	2.66×10^{-2}	5.08
140 mg/mL BSA	2.73×10^{-2}	5.21
100 mg/dL Glc	1.07×10^{-2}	2.04
200 mg/dL Glc	1.06×10^{-2}	2.03
0.2 mol/L PBS, 100 mg/dL Glc, 70 mg/mL BSA, pH 7.4	3.23×10^{-1}	61.6

* D_0 refers to the D value in pure water.

3.3.2.1. The ion strength dependence. As shown in Fig. 6a, the drug release rises notably with the increase of the ion concentration of the external phase. When the NaCl concentration changes from 0 to 0.2 mol/L (close to the salt concentration in body fluid), the release percentage during 12 h increases from 1.52% to 22.92%, that is, 4.5 mg/g and 67.4 mg/g dry membrane. And the value reaches 46.02% (135.3 mg/g dry membrane) in 2.0 mol/L NaCl. These results strongly suggest that the electrostatic interaction plays an important role in SA^- release from the AEHFMs. The release percentage values here are similar or lower than other reported values, confirming further the high effectiveness of drug release retarding. For example, the release contents of SA^- from Smopex®-103pe

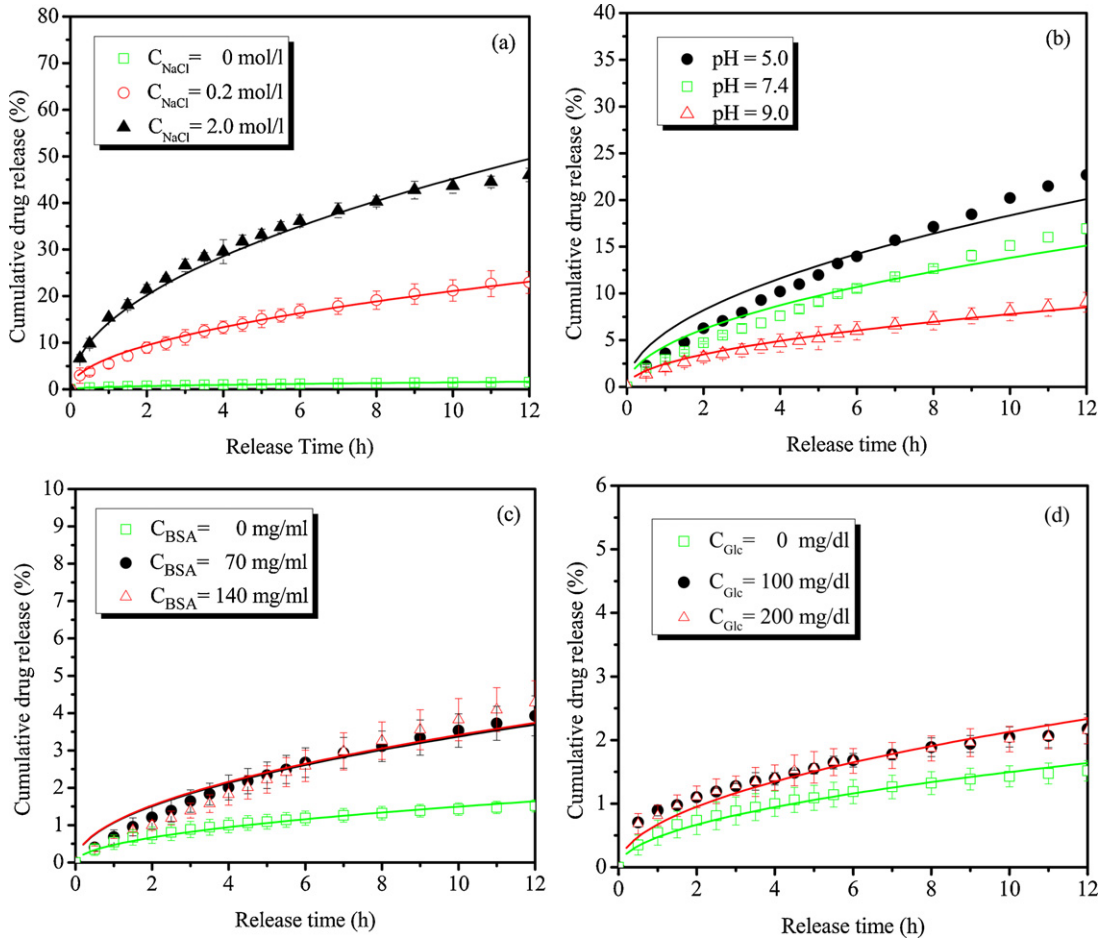

Fig. 6. Release behaviors of salicylate (SA^-) from BPPO-γ-MPS(+)-SA^- complexes at 37 °C: (a) with different ion concentrations (range from 0 to 2.0 mol/L) of the external phase; (b) with different pH conditions (range from pH 5.0 to 9.0) of the external phase; (c) with different BSA concentrations (range from 0 to 140 mg/mL) and (d) with different glucose concentrations (range from 0 to 200 mg/dL).

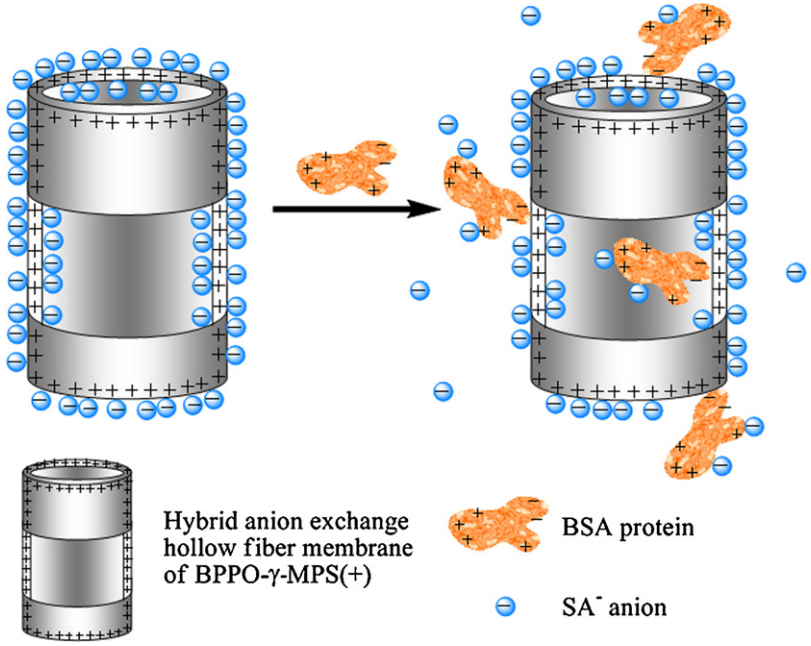

Fig. 7. Proposed interactions among the BPPO-γ-MPS(+) HFM, BSA, and SA^- anions.

and Smopex DS-218v anion exchange fibers are around 18% and 40% (40.3 mg/g and 89.7 mg/g dry membrane) respectively, in 0.0093 mol/L NaCl solution after 24 h (Hanninen et al., 2005). And the gelled microemulsions prepared by Feng et al. exhibit at least 44% drug release in PBS in 12 h (Feng et al., 2009).

3.3.2.2. The pH dependence. The pH dependence of the release of SA^- from BPPO-γ-MPS(+)-SA^- is shown in Fig. 6b. The release of SA^- in 12 h decreases from 22.68% (66.7 mg/g dry membrane), 16.93% (49.8 mg/g) to 9.06% (26.6 mg/g) as pH increases from 5.0, 7.4 to 9.0. These results indicate that the controlled release of the ionic drugs from BPPO-γ-MPS(+) depends on the pH condition of the external phase to a great extent. The reason is that, at lower pH condition (pH 5.0), the protonation of the carboxylate group of SA^- anions reduces the electrostatic interactions between the quaternary amino groups of the membrane and the carboxylate groups of the drug, and thereby increases the release rate of SA^-. At higher pH condition (pH 9.0), the phenolic hydroxyls of SA^- anions are partly deprotonated, which can enhance the electrostatic interactions between the drugs and the membrane. As the pH dependence of the drug release, the membrane has the potential to be applied as a pH-sensitive drug delivery vehicle for controlled drug release in ruminant animals, similar to the flat membranes reported by Hu and Dickson (Hu and Dickson, 2009).

3.3.2.3. The protein concentration dependence. Proteins and sugars, as common components in animal and human body, can potentially affect the process of drug delivery. Therefore, the experiments of protein and sugar concentration dependence have been carried out. Bovine serum albumin (BSA) is a transport protein and has similar functions as human serum albumin (HSA). Hence, it is used for the research of *in vitro* release behaviors. The concentration of 70 mg/mL is chosen so as to simulate the physiological condition. For comparison, concentration of 140 mg/mL (twice of the con-

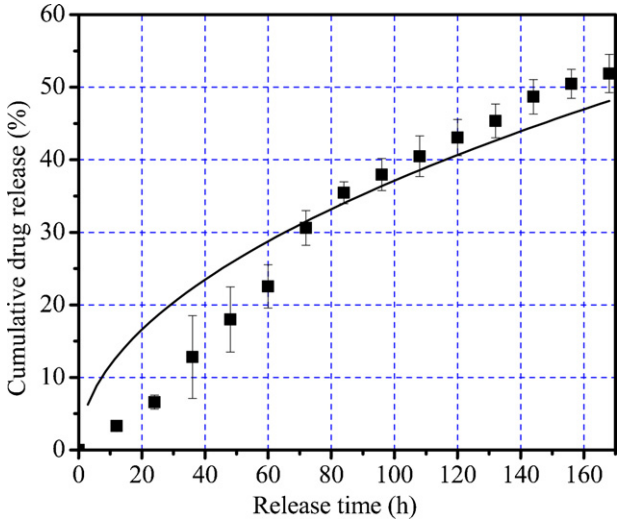

Fig. 8. Release behaviors of salicylate (SA^-) from BPPO-γ-MPS(+)-SA^- complexes at 37 °C in a simulated body fluid (0.2 mol/L PBS with 100 mg/dL glucose and 70 mg/mL BSA, at pH 7.4).

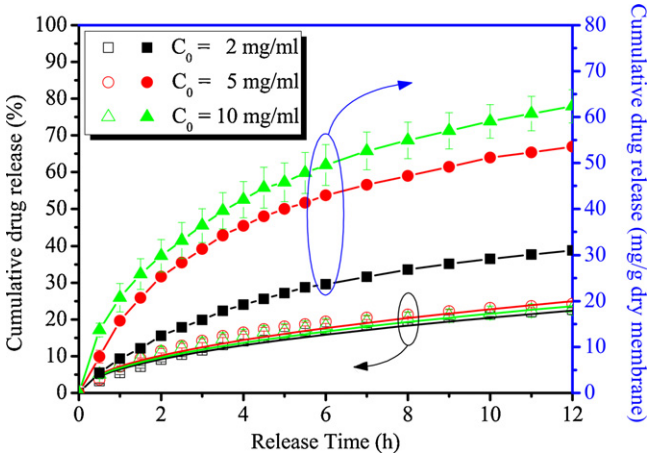

Fig. 9. Release behaviors of salicylate (SA^-) from BPPO-γ-MPS(+)-SA^- complexes with different drug loading in 0.2 mol/L NaCl solution at 37 °C. c_0 means the original NaSA concentration in the loading solution.

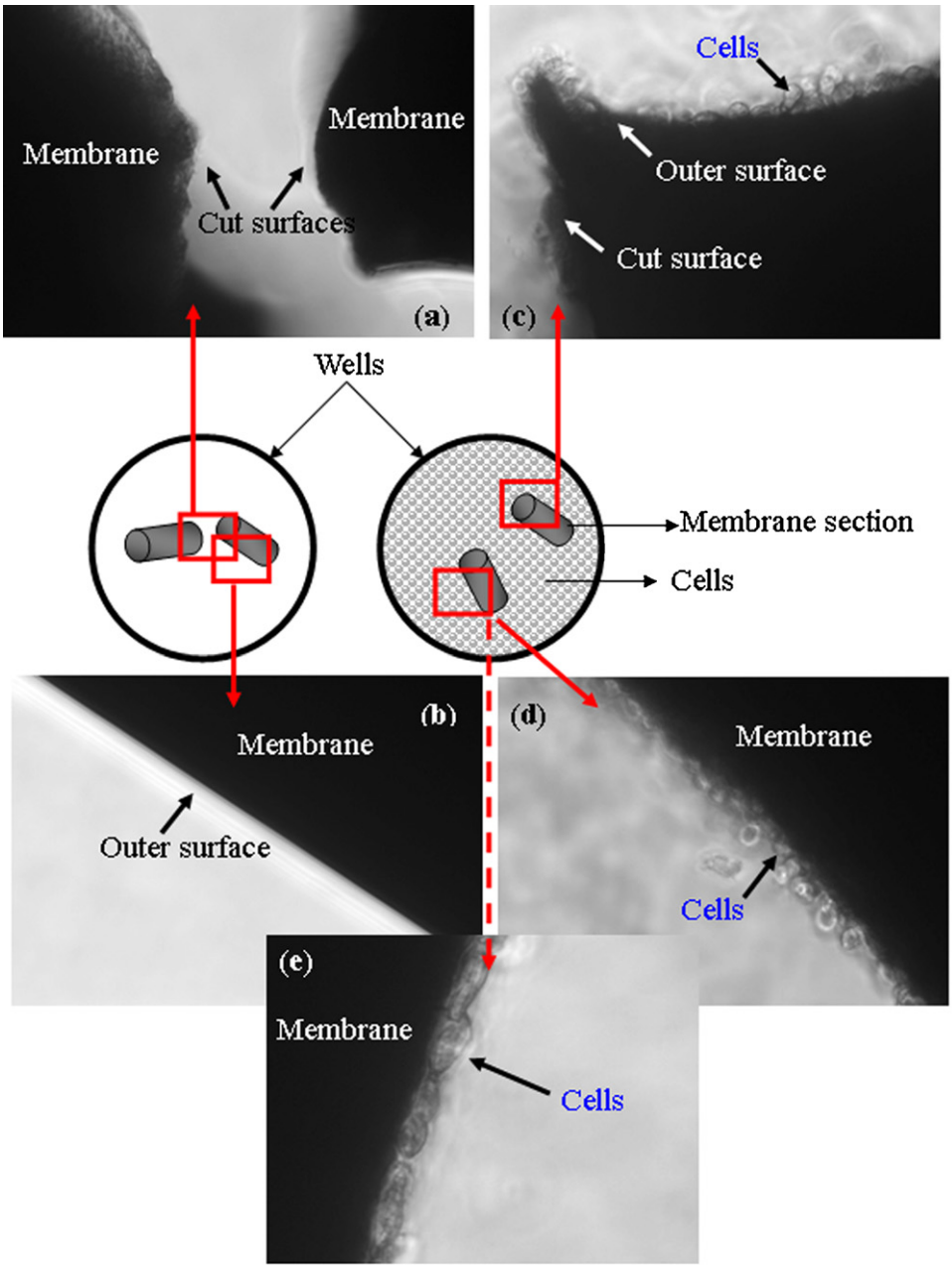

Fig. 10. Growth of HeLa cells incubated with BPPO-γ-MPS(+) HFM sections: (a) and (b) The membrane sections immersed in cell culture medium; (c) and (d) Cells attached to the membrane surface after 48 h (c with both cut and outer surface); (e) Cells attached to the membrane surface after 72 h.

centration in human blood) has also been investigated. The data obtained here will provide guiding clues for future *in vivo* studies. One point that should be noted is that there may be interaction strength between BSA and SA^- anions, and the detected amount of the drug out of the dialysis bag may be lower than the actual amount of drug released. Therefore, a control experiment has been performed to find the binding of BSA with SA^- anions. The result shows that 2.59 mg and 3.78 mg free SA^- anions are bound with BSA in 70 mg/mL and 140 mg/mL BSA solution (5 mL), respectively. The values are relatively small. For convenience of discussion, the binding of BSA with SA^- anions is not taken into account in our following sections.

As shown in Fig. 6c, about 3.93% (11.6 mg/g dry membrane) of SA^- is released in 12 h under 70 mg/mL BSA and 4.28% (12.6 mg/g) under 140 mg/mL. These values are similar with each other and higher than that in absence of BSA. This indicates that: (1) the presence of BSA can promote the drug release and (2) at high BSA concentration (≥70 mg/mL), further increase of BSA will not affect obviously the release performances. For explanation of the above phenomenon, different interaction patterns (Hu et al., 2009) among protein, drug and drug vehicle can be modified and used here. Fig. 7 is the illustration of the different interaction patterns. The surface of BSA possesses both anionic groups and cationic groups. On one hand, the anionic groups can interact with the quaternary amino groups of BPPO-γ-MPS(+) through electrostatic interactions. As a result, the electrostatic interaction between the membrane and drugs is disturbed, which leads to improvement in the release rate of the drugs. On the other hand, the cationic amine groups of BSA can bind SA^- anions and the hydrophobic interior of the protein can encapsulate SA^- anions by hydrophobic interactions, both of which could retard the release of the drug into the external phase. The concurrent action of the above promoting and retarding effects

causes the irregular change of the drug release value with different BSA concentrations.

3.3.2.4. The sugar concentration dependence. Glucose is chosen as the model sugar. Its concentration is set as 100 mg/dL and 200 mg/dL to represent the blood sugar conditions of healthy humans and diabetics respectively, since the plasma glucose level in healthy human body is 90–130 mg/dL (pre-meal) or less than 180 mg/dL (post-meal) (Association, 2006).

Fig. 6d illustrates that the presence of glucose can slightly improve the release rate of SA^- from BPPO-γ-MPS(+)-SA^-. The polarity of glucose and the hydrogen bonding between the drug and glucose may disturb the interaction between the drugs and the membrane, and hence the release of the entrapped drugs is increased. Another finding from Fig. 6d is that increase of glucose concentration from 100 mg/dL to 200 mg/dL causes no significant change of the drug release value. Therefore, the drug release system can be adapted to both non-diabetics and diabetics. And this result is very significant for future clinical applications.

As a conclusion, Fig. 6a–d shows that the ion concentration and pH condition of the external phase have pronounced effects on the release of the drug (SA^-), while the presence of protein and sugar can slightly improve the release rate. These results suggest the importance of the electrostatic interaction between SA^- and the BPPO-γ-MPS(+) membrane.

3.3.3. The release behavior in a simulated body fluid

In general, the ionic strength, protein and sugar concentrations of the body fluid are relatively constant. Therefore, one long-period release experiment in a simulated body fluid (0.2 mol/L PBS, 100 mg/dL Glc, 70 mg/mL BSA, pH 7.4) is carried out to forecast the *in vivo* performance of BPPO-γ-MPS(+)-SA^-.

As shown in Fig. 8, 51.89% (152.6 mg/g dry membrane) of SA^- is released from BPPO-γ-MPS(+)-SA^- in 168 h (7 days). And the diffusion coefficient (D) is calculated to be 0.32 cm^2/s, lower than that in naked NaCl solution (1.04 cm^2/s, Table 2) of the same ion strength. This is unexpected, since the above result has proved that the presence of BSA or sugar can slightly improve the release rate. Concurrent actions of protein, sugar, salt with the membrane and the drug should be responsible for such abnormity. Besides, presence of BSA and glucose can lead to higher viscosity of the external phase. Hence, the activity of the drug molecules may be decreased and their release rate is reduced accordingly.

As mentioned in the Section 1, side effects caused by systemic or intra-articular administration have limited the clinical applications of many NSAIDs including NaSA. Our result shows that SA^- loaded onto BPPO-γ-MPS(+) can release continuously and slowly at least over 7 days in the simulated body fluid. Therefore, BPPO-γ-MPS(+) has the potential to be a drug carrier for NaSA for anti-inflammatory devices. Steady drug blood concentration can be obtained during a relatively long period, leading to simplified dosing schedule, reduced side effects, improved patient compliance and drugs bioavailability.

3.3.4. Release behaviors of BPPO-γ-MPS(+)-SA^- with different drug loadings

The release behaviors of BPPO-γ-MPS(+)-SA^- with different drug loadings have been observed. As illustrated in Fig. 9, the absolute amount of drug released in 0.2 mol/L NaCl solution is in the range of 34.5–69.1 mg/g dry membrane, which are similar to the value previously reported (40.3–89.7 mg/g in 0.0093 mol/L NaCl solution) (Hanninen et al., 2005).

In Fig. 9, the absolute amount of drug released follows an increasing trend as the concentration of loading solution increases. This means higher drug loading can lead to a larger amount of drug released. Therefore, a proper drug loading should be chosen to achieve the effective dose of drug, but not to cause excessive release which may lead to side effects.

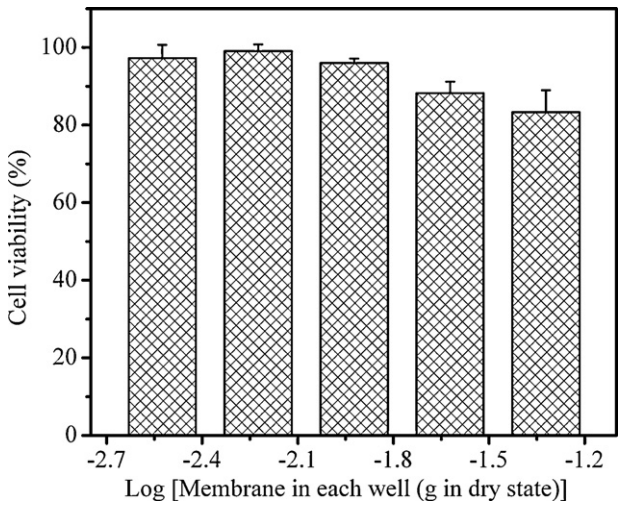

Fig. 11. Cytotoxicity of BPPO-γ-MPS(+) HFM towards HeLa cells after 24 h of incubation determined by an MTT assay. Membrane mass in each well is expressed as logarithmic form.

Fig. 9 also illustrates that the increase of drug loading causes no significant change of the percentage of drug released. The diffusion coefficients (D) are calculated through fitting the drug release percentage – time curve by Higuchi equation (Eq. (3)). Thus the D values of the BPPO-γ-MPS(+)-SA^- complexes with different drug loading are similar to each other (from 0.98 to 1.21 cm^2/s). Therefore, for a certain model drug, the release rate (represented by D value) is mainly related to the physicochemical properties of the drug carrier and the external phase conditions, but not the drug loading content.

3.4. Biocompatibility

As a potential implant biomaterial, the biocompatibility of BPPO-γ-MPS(+) HFMs must be ensured before the applications. Here the growth of cells on the surface of BPPO-γ-MPS(+) has been observed and the cytotoxicity studies have been conducted.

Fig. 10a and b shows the cut surfaces and the outer surfaces of membrane sections in cell culture medium containing no cells. Fig. 10c–e are the photos of the cells incubated with the surfaces of membranes for 48 h (c with both cut and outer surface) or 72 h, respectively. The borderlines of the membranes in Fig. 9a and b are smooth and clear. The surfaces of the membranes in Fig. 9c and d are attached with many cells, indicating that the cells have found attachment points on the surface of the membranes and remained alive during 48 h instead of being poisoned. After further 24 h, the cells adhered on the membranes are still alive, as can be seen in Fig. 10e. Thus, we can generally conclude that, the BPPO-γ-MPS(+) HFMs are nontoxic or low-toxic to HeLa cells and can well support the cells adhesion. The adhesion of cells should be due to the characterizations of BPPO-γ-MPS(+) surfaces, since it's been well accepted that cells tend to adhere onto the ionic, hydrophilic, and solid surfaces (Maroudas, 1977).

The result of the cytotoxicity studies by MTT assay is shown in Fig. 11. BPPO-γ-MPS(+) displays high cell viability (≥80%) after 24 h, suggesting the low cytotoxicity of the membrane. As the density of BPPO-γ-MPS(+) increases from 0.003 to 0.048 g/well, the cell viability decreases slightly. This is probably attributed to the decrease of cells number, because a small number of cells are taken out along with the membrane sections before MTT is added. Overall, the membrane is biocompatible as a potential implanted drug carrier for controlled release.

4. Conclusions

Hybrid AEHFM of BPPO-γ-MPS(+) is prepared by hybridization with γ-MPS. The dimensional stability is increased, and the swelling is suppressed as compared with BPPO(+) membrane without hybridization (DCR value decreased from 34.2% to 12.9%), which is advantageous for the retarding of NaSA release (drug release content decreased from 2.93% to 1.52% in pure water in 12 h).

The loading capability of BPPO-γ-MPS(+) for SA^- (q_m = 396.9 mg/g) is higher than some reported drug reservoir materials, such as anion exchange fibers, flat membranes and some other polymer materials. The loading content can be controlled by changing the original drug concentrations, ion concentrations or loading time. The release behaviors of BPPO-γ-MPS(+)-SA^- mainly depend on ion concentration and pH condition of the external phase, because the electrostatic interaction plays very important role in the binding of the drug onto BPPO-γ-MPS(+) membrane. And the pH dependence of the release behavior indicates the potential of the membrane as a pH-sensitive drug delivery vehicle. Furthermore, the drug release system can be adapted to both non-diabetics and diabetics since the effect of the plasma glucose level on the release rate is little. In a simulated body fluid, BPPO-γ-MPS(+)-SA^- can release SA^- at a relatively slow rate during 7 days (51.89% drug released in 7 days, $D = 0.3225\ cm^2/s$, neglecting the drug bound by BSA). Moreover, the membrane displays proper biocompatibility as revealed by the cell adhesion and cytotoxicity studies. These results suggest that the material of BPPO-γ-MPS(+) is a promising drug reservoir material for NSAIDs delivery. Further investigations of the release behaviors of other drugs and chemicals by such kind of membrane are under way and the findings are to be presented in our future work.

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