International Journal of Adhesion & Adhesives 48 (2014) 217–223

Contents lists available at ScienceDirect

International Journal of Adhesion & Adhesives

journal homepage: www.elsevier.com/locate/ijadhadh

Fabrication of pH sensitive amphiphilic hot-melt pressure sensitive adhesives for transdermal drug delivery system

Xiao Tong [a], Qing Wang [a,*], Hai-xia Wang [a], Xiao-Hui Li [b,**], Wei Wu [c], Xin-yi Che [a]

[a] School of Pharmaceutical Science and Technology, Dalian University of Technology, No. 2 Linggong Road, Ganjingzi District, Dalian City 116024, Liaoning Province, PR China
[b] School of Life Science and Biotechnology, Dalian University of Technology, PR China
[c] Sixth Pharm Factory, Harbin Pharmaceutical Group, PR China

ARTICLE INFO

Article history:
Accepted 1 July 2013
Available online 5 October 2013

Keywords:
SIS
Eudragit® EPO
Amphiphilic structure
TDDS

ABSTRACT

Based on the blend of styrene-isoprene-styrene (SIS) thermoplastic elastomer and acrylic resin Eudragit® EPO, amphiphilic hot-melt pressure sensitive adhesives (HMPSAs) were fabricated. Compatibility and micromorphology of SIS/EPO blends (SEBs) were analyzed with differential scanning calorimetry (DSC), atomic force microscopy (AFM) and scanning electron microscopy (SEM). The results showed that when the mass ratio of SIS to EPO was 1:1～1:2, bicontinuous structure was formed. Following the addition of an appropriate amount of polyethylene glycol (PEG), mineral oil and C_5 resin, the amphiphilic HMPSAs were prepared. Because of the compatibility between SIS and EPO, as well as the hydrogen bond interaction between EPO and PEG, amphiphilic HMPSAs showed good thermostability. The adhesive performance of HMPSAs was measured with 180° peeling strength and holding power. Geniposide and oleanolic acid were used as model drugs to investigate drug release behavior. When the mass ratio of PEG to SEB was 13:30～16:30, the HMPSAs could maintain good adhesion performance and achieve continual release of both hydrophilic and lipophilic drugs. In weakly acidic conditions, the HMPSAs exhibited good hygroscopicity and release profile, it was shown that pH sensitive amphiphilic HMPSAs were more suitable for transdermal drug delivery system (TDDS).

1. Introduction

TDDS is a method which administrates drugs through the skin. Drugs pass trough stratum corneum, diffuse through the skin and enter systemic blood circulation through adsorption by the capillary. Compared to the common oral and injectable administration, TDDS has the advantages of avoiding gastrointestinal irritation, and by-passing hepatic first-pass effect, maintaining a constant blood concentration over extended period of time, compliance of patients use, etc. The patch is a common TDDS formulation which consists of the backing layer, pressure sensitive adhesive and release liner. The pressure sensitive adhesive not only helps skin adhesion, but also commonly plays an important role in solubilizing and releasing the drug, thereby making it an important part of TDDS [1].

HMPSAs have become one of the most important pressure sensitive adhesives in use, due to their advantages of being solvent-free, minimal environmental concern and safe production methods [2]. SIS-based HMPSAs are prepared with SIS thermoplastic elastomers, tackifying resins and plasticizers [3]. Due to their strong cohesion and high drug loading, HMPSAs are suitable for use as the matrix of the patch [4].

However, since SIS is very hydrophobic, HMPSAs prepared with SIS can only be applied for lipophilic drugs and usually lead to skin irritation, which greatly restricts their application in TDDS. By epoxidizing the double bonds on isoprene block of SIS, its polarity can be improved, but due to epoxidization, the compatibility between SIS and tackifying resin is reduced and the brittleness of HMPSAs is increased [5], which will reduce the adhesion performance of the HMPSAs. Physical methods can also be used to improve the hydrophilic nature of HPMSAs. Li-li Hua et al. prepared HMPSAs through melt blending SIS and Eudragit® RLPO which improved the hydrophilic nature and maintained good adhesive performance [6].

Meanwhile, pH is also an important factor in TDDS, which will not only affect drugs passing through the skin [7,8], but also alter the drug release profile in the pressure sensitive adhesive [9]. Skin surface turns out to be weakly acidic [10], making the selection of an appropriate pressure sensitive adhesive, which can optimize the drug release profile, was an important avenue to develop suitable TDDS.

* Corresponding author. Tel.: +86 411 8498 6176.
** Corresponding author. Tel.: +86 411 8470 6326.
E-mail addresses: qwang@dlut.edu.cn (Q. Wang), Lxhxh@dlut.edu.cn (X.-H. Li).

0143-7496/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijadhadh.2013.09.025

In this study, the acrylic resin Eudragit® EPO with tertiary amine group was blended with SIS as skeleton, following the addition of PEG, mineral oil and C_5 resin to form the amphiphilic HMPSAs. The adhesive performance of HMPSAs was measured with 180° peeling strength and holding power. Geniposide and oleanolic acid were used as model drugs to investigate release behavior of hydrophilic and lipophilic drugs, respectively. Moreover, taking into account that the pH-sensitivity of tertiary amino groups of EPO [11], different drug release behaviors were investigated under the conditions of different pH.

2. Experimental

2.1. Materials

SIS thermoplastic elastomers (YH-1105, Mn$\sim 8\times10^4$, styrene 15 wt%, Sinopec Baling Petroleum & Chemical Co. Ltd, China), Eudragit® EPO (Mn$\sim 1.5\times10^5$, Evonik Industries, Germany), Polyethylene glycol 6000 (PEG_{6000}, Sinopharm Chemical Reagent Co. Ltd, China), C5 resin (C-100R, Eastman Chemical Company, USA), mineral oil (KN-4010, Kelamayi refinery, China), and antioxidant Irganox 1010 (from Beijing jiyi chemical limited company, China) were used in this study. Geniposide (Nanjing Zelang Medical Technology Co. Ltd, China) and oleanolic acid (Nanjing Qingze Medical Technology Co. Ltd, China) were model drugs to investigate release behavior. Their physical and chemical properties are displayed in Table 1.

2.2. Preparation of SEBs

MS-II small blend extrusion testing machine (Beijing University of Aeronautics and Astronautics, China) was preheated to 180 °C, then 2 g of SIS and 2 g of EPO was added. SEB with the weight ratio of 1:1 of SIS to EPO was prepared at a stirring speed of 300 rpm for 10 min. Then the mass of SIS and EPO was adjusted and a series of SEBs were prepared by melt-blending SIS and EPO with the weight ratio of 3:1, 2:1, 1:2, 1:3, 1:4 and 1:5.

2.3. Differential scanning calorimetry (DSC)

Samples were characterized with DSC (TA Q2000 DSC, USA). 10 mg of SEBs prepared in 2.2 were taken to alumium crucible. These samples were first heated to 150 °C at a heating rate of 10 °C/min and kept at 150 °C for 10 min. Then, they were cooled to −100 °C at a rate of 10 °C/min and kept at −100 °C for 5 min. The thermal history was eliminated. Finally, they were reheated to 150 °C at a heating rate of 10 °C/min. All tests were taken in N_2 stream at speed of 10 mg/min and subject to the second resultant curve performance.

2.4. Atomic force microscopy (AFM)

SEBs prepared in 2.2 were heated to 150 °C and softened. Then they were covered with a layer of polyethylene terephthalate (PET) film. A steel plate was pressed on them and pushed down until the blends were compressed into a film about 100 μm in thickness. It was allowed to stand at room temperature for 24 h before characterized with CSPM5500 scanning probe microscope (Guangzhou Primitive Nano Instrument, China). AFM was performed at room temperature at the frequency of 1 Hz in tapping mode with scanning range 50 nm or 5000 nm. RH < 40%.

Table 1
Physical and chemical properties of model drugs.

Drug	log *P*	Molecular weight	Melting point/ °C
Geniposide	−0.968	388	164
Oleanolic acid	9.059	456	309

2.5. Scanning electron microscopy (SEM)

Some SEBs prepared in 2.2 were selected to froze in liquid nitrogen for 4 h, then rightly freeze-fractured. Their freshly-fractured surfaces were sputter-coated with gold before they were characterized with JSM-5600LV scanning electron microscopy (JEOL, JP) for their morphologies at 15 kV.

2.6. Preparation of amphiphilic HMPSAs

GSH-01 reaction kettle (Weihai Hangyu Chemical Test Instruments Co., Ltd, China) was preheated to 150 °C. Nine gram of SEBs prepared in 2.2 were put into the reaction kettle and then stirred for 10 min in 300 rpm. Then 5 g C5 resin, 2 g mineral oil and a certain amount of PEG (Table 2) were added to the kettle. After stirring for 20 min at a speed of 300 rpm, amphiphilic HMPSAs were prepared.

TX2003-1 hot melt coater (TongXu drug delivery technology Institute of Dalian University of Technology, China) was used. The amphiphilic HMPSAs were hot coated on PET film of 100 ± 20 μm in thickness at 140 °C. After cooling, the backing layer was pressed to obtain the blank patches.

Amphiphilic HMPSAs were heated to 140 °C and softened. Then 2 wt% model drug geniposide or oleanolic acid was added and stirred for 20 min at 300 rpm to dissolve. Then the drug-loaded patches were achieved.

2.7. 180° peel strength

The blank patches prepared in 2.6 were cut into strips with 25 mm × 100 mm in dimension. Then a roller weighted 2 kg was used to press the patch on a clean stainless steel substrate for three times. The specimens were tested with a BLD-S electronic all-powerful stripping machine (Labthink Instruments Co., Ltd, China) at a peeling rate of 300 mm/min. Each set of experiment had three specimens tested and the reported data was their average. All the tests were taken under the conditions of 23 ± 2 °C and RH 65 ± 5%.

2.8. Holding power

The blank patches prepared in 2.6 were cut into strips with 25 mm × 70 mm dimension. Then a roller weighted 2 kg was used to press the patch across two cleaned stainless steel substrates to bond them together. Their holding power was measured with a CZY-6 holding adhesive testing instrument (Labthink Instruments Co., Ltd, China) under a load of 1 kg. Each sample had three specimens measured and the reported data was their average. All the tests were taken under the conditions of 23 ± 2 °C and RH 65 ± 5%.

2.9. Drug release experiments

In vitro drug release experiments were carried out using KX-5P Permcell horizontal diffusion cells (Dalian Kexiang Instruments Co., Ltd, China). The instrument has two half-cells with a water

Table 2
Weight of PEG in HMPSAs.

	1	2	3	4	5	6	7	8	9
PEG/g	0	1.2	2.4	3.6	3.9	4.2	4.8	6.0	7.2

jacket connected to a water bath at 37 ± 0.5 °C. Each half-cell has a volume of 5 ml, filled with receptor solution. The drug-loaded patches prepared in 2.6 were exposed to face the receptor solution and the release area was 0.627 cm^2. The receptor cells were placed on a magnetic stirrer and stirred at a speed of 700 rpm. 0.2 ml receptor solution was withdrawn from the cell at 1, 3, 6, 9, 12 and 24 h, replaced immediately by the same amount of fresh receptor solution.

Receptor solution for drug-loading patches which containing geniposide is PBS buffer of 5.0, 6.0 and 7.0 in pH. And receptor solution for drug-loading patches which containing oleanolic acid is ethanol/water solution (40:60, v/v). Their concentration (Cn) was determined by high performance liquid chromatography (HPLC). Drug cumulative release rate (Q) was calculated using the following equations:

$$M_t = \frac{(C_n V + \sum C_{n-1} 0.2)}{A} \quad (1)$$

$$Q = \frac{M_t}{M_\infty} 100\% \quad (2)$$

where M_t is the cumulative amount of drugs released in unit area. C_n is the concentration of the Nth sample. V is the volume of receptor solutions. A represents release area. M_∞ is the content of drugs in unit area.

2.10. HPLC analysis

A Shimadzu instrument (LC2010A, LC solution workstation) and a Agilent C_{18} column (5 μm, 4.6 mm × 150 mm) were used in HPLC analysis. The column was maintained at 30 °C and the flow rate was 1.0 ml/min. The volume of injection was 20 μl.

The mobile phase of geniposide was acetonitrile–purified water (12:88, v/v) and the UV detector was set at 240 nm. The calibrations curve was constructed to determine the drug concentration in the range of 0.5–40 μg/ml and $R^2 = 0.9996$. While the mobile phase of oleanolic acid was acetonitrile-1% phosphoric acid aqueous solution (85:15, v/v) and the UV detector was set at 210 nm. The calibrations curve was constructed to determine the drug concentration in the range of 0.5–30 μg/ml and $R^2 = 0.9992$.

2.11. Water absorption experiments

The blank patches prepared in 2.6 were cut into slices (2 cm × 2 cm). Release liner was uncovered and the patches left were weighed (W_1). Patches without release liner were mounted on release nets of a dissolution tester (ARX-6G, Tianjin Tianda Tianfa Instruments Co., Ltd, China) downward. Then the release nets were put in release cup which was filled with PBS solution (pH in 7.0, 6.0 and 5.0). The paddle rotation was set up at 40 rpm and the temperature was maintained at 37 °C. Patches were taken out to measure their weight (W_2) accurately after removing excess solution by filter papers at 1, 3, 6, 9, 12 and 24 h, which should be processed within 20 s. The entire sampling process should be as fast as possible to reduce the operation error. According to the data, the following equation is used to obtain water absorption (W%) of the patches.

$$W\% = \frac{W_2 - W_1}{W_1} 100\% \quad (3)$$

2.12. ^1H nuclear magnetic resonance spectroscopy (^1H NMR)

The amphiphilic HMPSAs were immersed in a PBS solution of pH 7.0,6.0 and 5.0 for 24 h. After that, they were dried to constant weight at 80 °C and each dissolved in deuterated chloroform ($CDCl_3$). Bruker Avance II 400 NMR spectrometer (Swiss Bruker instruments Inc.) was used for analyzing the samples. The chemical shift value was recorded according to relative displacement of tetramethylsilane (TMS, internal standard).

3. Results and discussion

3.1. Compatibility between SIS and EPO

The compatibility of polymers can be characterized with its glass transition temperature (Tg) measured by DSC. Fig. 1 and Table 3 shows the DSC curve of SEBs in different proportion and the corresponding parameters. SIS has two glass transition temperatures polyisoprene (PI) phase $Tg_1 = -57.8$ °C and polystyrene (PS) phase $Tg_2 = 84.8$ °C while EPO only has one glass transition temperature $Tg_3 = 54.7$ °C.

After SIS and EPO were blended, results showed that Tg_1 which loaded in low-temperature region was almost constant. Tg_2 became blurred probably due to the lower proportion of PS and influence of the EPO mixed and Tg_3 showed slight shift to the high temperature with the increase of SIS. DSC analysis showed that the SIS and EPO have a certain degree of compatibility. Compatibility of SIS and EPO can also be explained by thermodynamics of the polymer solution: the solubility parameters (δ) of PS and PI are 18.7 and 16.6 $MPa^{1/2}$, respectively [12], while the solubility parameter of EPO is calculated to be 19.6 $MPa^{1/2}$ [13]. Because of the solubility parameters of PS and EPO are more similar, EPO and PS have better compatibility.

Atomic force microscopy (AFM) was used to further investigate the microstructural feature of the sample. SIS showed that the bright spots of PS were dispersed in the dark PI as "sea-island" structure (Fig. 2a). After EPO was added, PS phase became larger and interface of PS and PI became blurred (Fig. 2b). That indicates EPO can partly dissolving in the PS phase which means a of EPO

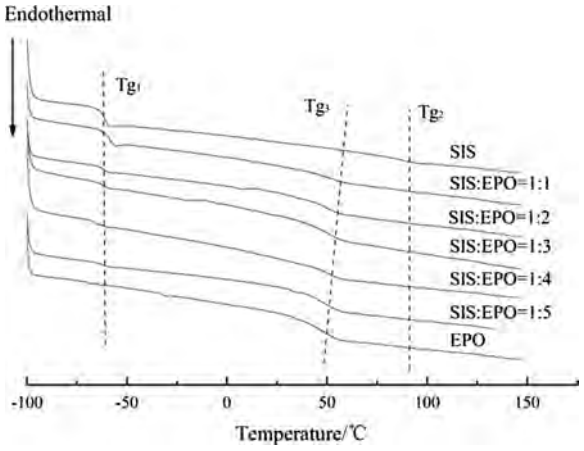

Fig. 1. DSC curves of SIS, EPO and SEBs.

Table 3
Glass transition temperatures (Tg) of SIS, EPO and SEBs.

SIS:EPO	Tg_1 (°C)	Tg_2 (°C)	Tg_3 (°C)
1:0	−57.8	84.8	–
1:1	−56.5	–	57.9
1:2	−55.8	–	57.1
1:3	−55.4	–	56.5
1:4	−55.1	–	55.2
1:5	−54.6	–	54.9
0:1	–	–	54.7

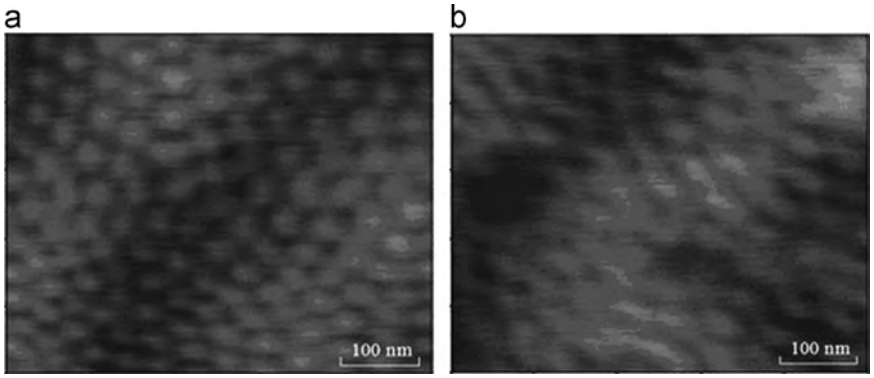

Fig. 2. AFM images of (a) SIS and (b) SEB.

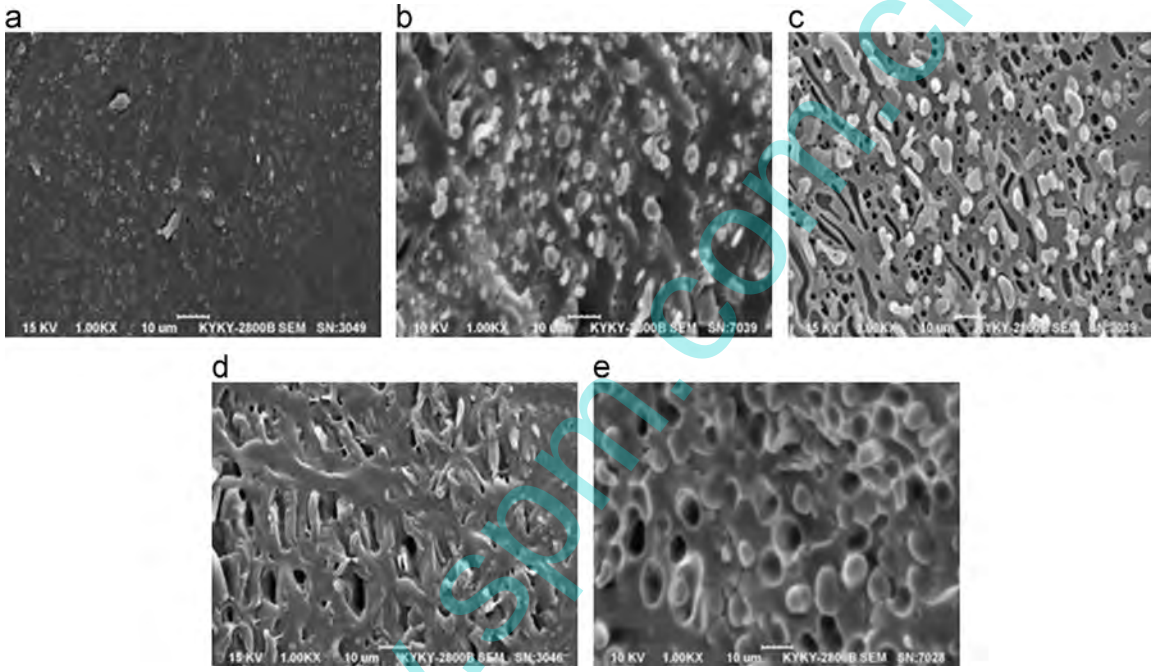

Fig. 3. SEM images of SEBs (a) SIS:EPO=3:1, (b) SIS:EPO=2:1, (c) SIS:EPO=1:1, (d) SIS:EPO=1:2, and (e) SIS:EPO=1:3.

and PS. The n-π interactions between the ester groups of EPO and benzene rings of PS might be the reason of their good compatibility and made this skeleton show good thermostability [14].

3.2. Microstructure of SEBs

Scanning electron microscope (SEM) was used to observe the microstructure of the blends. When the relative ratio of the SIS in the mixture was high, EPO distributed themselves in the SIS phase (Fig. 3a). the domain size of EPO became larger with the EPO content increasing (Fig. 3b). When the weight ratio of SIS to EPO becomes 1:1∼1:2, EPO gradually forms continuous phase, showing the formation of a bicontinuous structure (Fig. 3c and d). Further increase of EPO reversed the scenario, with EPO being a continuous phase and SIS being dispersed in EPO phase (Fig. 3e).

The interface of SEB (SIS:EPO=1:2, w/w) was also observed by AFM and compared with SIS and EPO (Fig. 4). It can be observed that when the SIS and EPO blended with the mass ratio of 1:2, the blend shows a bicontinuous structure.

When the weight ratio of SIS to EPO was 1:1∼1:2, SEB formed a bicontinuous structure, so further experiments kept SIS and EPO in a mass ratio of 1:2. The acrylic resin EPO has a good compatibility with PEG [15]. Adding PEG to the SEB, a hydrophilic channel can be postulated to form, which could be expected to increase the drugs release kinetics but also reduce the side-effects of skin irritation via the addition of biocompatible PEG.

3.3. Adhesive performance of amphiphilic HMPSAs

The adhesive performance of prepared HMPSAs was tested, including 180° peel strength and holding power. The results (Table 4) showed that the amphiphilic HMPSAs presented maximum 180° peel strength in the range of PEG:SEB=13:30∼16:30 (w/w) and subsequently reduced. It was speculated that when the amount of PEG was low, EPO was sufficiently diluted and dispersed uniformly in the matrix, so that the wettability was increased and adhesive strength was enhanced. A small amount of the free-state PEG would not significantly lower the adhesive strength of HMPSAs. While excess amount of PEG (PEG:SEB > 16:30, w/w) would reduce the adhesive property. Therefore the adhesive strength of HMPSAs decreases with increasing amount of PEG.

Due to the strong cohesion of SEBs and hydrogen bond interaction between EPO and PEG, when PEG:SEB ratio is smaller than 16:30 (w/w), the HMPSAs showed good holding power. But if

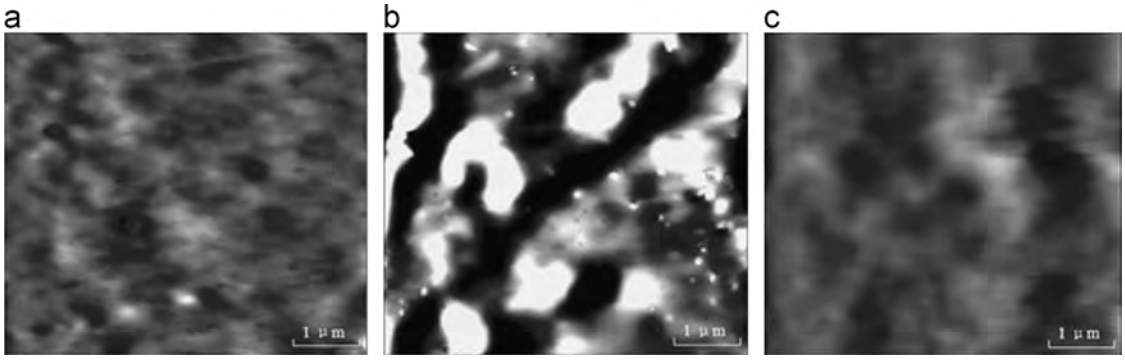

Fig. 4. AFM images of (a) SIS, (b) SEB and (c) EPO.

Table 4
Adhesive performance of HMPSAs.

	PEG:SEB[a]	180°Peel strength /KN/m	Holding power /h
1	Without PEG	0.11	> 48
2	4:30	0.12	> 48
3	8:30	0.12	> 48
4	12:30	0.14	> 48
5	13:30	0.15	> 48
6	14:30	0.15	> 48
7	16:30	0.17	> 48
8	20:30	0.09	21
9	24:30	0.05	7

[a] Weight ratio.

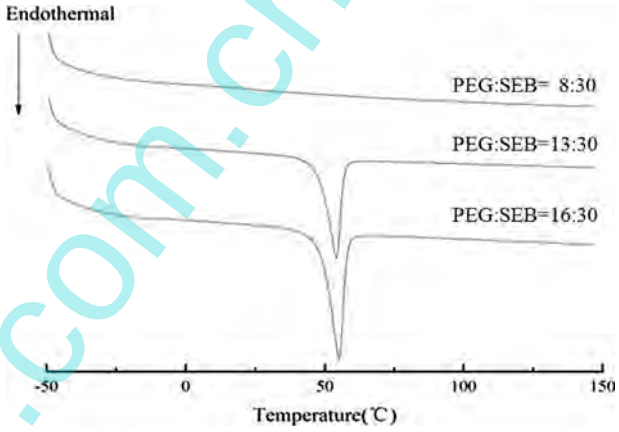

Fig. 6. DSC curves of HMPSAs.

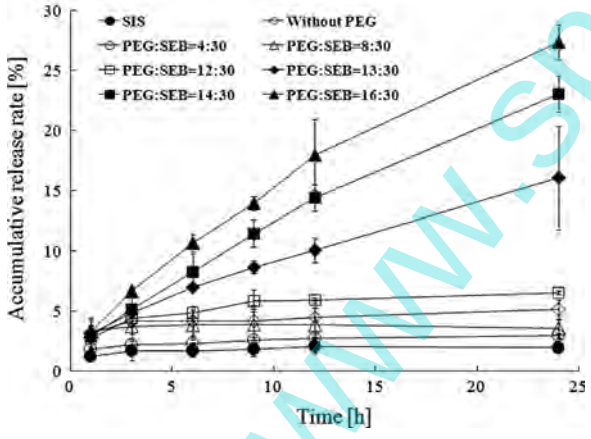

Fig. 5. Drug accumulative release curves of geniposide in HMPSAs (n=3).

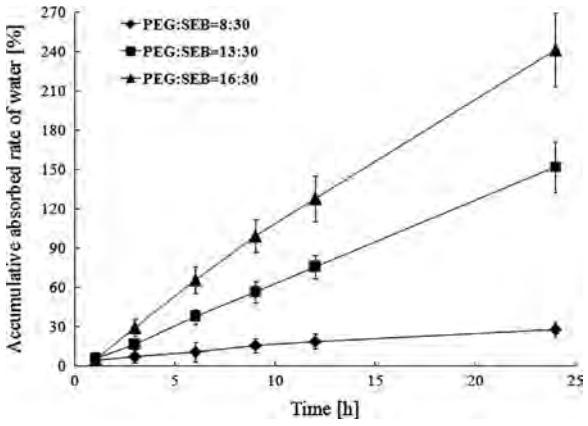

Fig. 7. Accumulative absorb curves of water in HMPSAs (n=3).

excess amount of PEG was used, it would reduce not only the cohesion but also the contact surface adhesion of HPMSAs, which may be caused by the low cohesion of PEG.

3.4. Drug release

Geniposide was used as hydrophilic model drug and its release profile was shown in Fig. 5. Compared to the SIS-based HMPSA, the accumulate release rates of geniposide in the SEB-based HMPSAs were increased, especially when PEG:SEB > 12:30.

Geniposide is very polar (log P = −0.968) and mainly dissolved in the EPO side chains and PEG domain. The PEG molecules were wrapped by EPO molecule chains when the amount of PEG was low. So the receptor solution could not enter into the HMPSAs and only a small amount of drug on the surface was released. As the amount of PEG increased, independent regions of PEG were formed, making receptor solution enter the HMPSAs through this "hydrophilic channel" and increased the release rate of geniposide.

Three kinds of amphiphilic HMPSAs (PEG:SEB = 8:30, 13:30 and 16:30, w/w) were used to perform differential scanning calorimetry (DSC) and water absorption experiment (pH = 7.0 PBS is used as experiment solution) to prove the above mentioned hypothesis. The results are shown in Figs. 6 and 7.

According to Fig. 6, there was no PEG melting peak when the amount of PEG was small, indicating that PEG was fully dispersed in EPO domain. When the amount of PEG was increased,

crystalline region of PEG formed and melting peak appeared at about 60 °C. At the same time, with low PEG amount, water absorption rate of patches was low. And as the amount of PEG increased (PEG:SEB=13:30∼16:30, w/w), high water absorption rate was observed. These phenomena were in consistent with what was described previously. The biocompatibility originated from PEG.

Oleanolic acid (log P=9.059) was used as the lipophilic model drug, it was shown that there is no significant statistical difference ($P>0.05$) in the accumulate release rates of Oleanolic from either SIS-based HMPSA or amphiphilic HMPSAs (Fig. 8).Therefore, when PEG:SEB > 12:30 (w/w), amphiphilic HMPSA can achieve balanced release of both hydrophilic and lipophilic drugs.

3.5. Influence of pH

About 50 wt% dimethylamino ethyl methacrylate block was present in EPO, giving EPO pH sensitive property. Taking into account of the weak acid environment of skin surface, we used pH=7.0, 6.0 and 5.0 PBS as receptor solution to investigate the drug release behavior.

When the amount of PEG was small, there was no obvious influence of pH on drug release (Fig. 9a). As the amount of PEG increased, receptor solution entered into the HMPSAs by the "hydrophilic channel". Comparing to pH=7.0, release rate of geniposide increased substantially while pH=5.0 due to the protonation of EPO (Fig. 9b and c). The protonation of EPO in HMPSAs was evaluated by ^{1}H NMR spectroscopy (Fig. 10). In the untreated HMPSA, the single peak located at 2.04 ppm is attributed to the hydrogen atoms of tertiary amino group in EPO. After the HMPSA was treated by pH=7.0 PBS, chemical shift of the single peak did not change. Whereas treated by pH=6.0 and 5.0 PBS, chemical shift of the single peak changed to 2.16 ppm (Fig. 10). This may be due to the protonation of tertiary amine group in HMPSAs in weakly acidic condition.

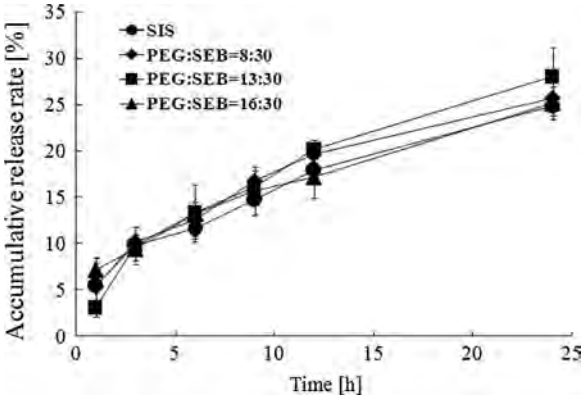

Fig. 8. Drug accumulative release curves of oleanic acid in HMPSAs (n=3).

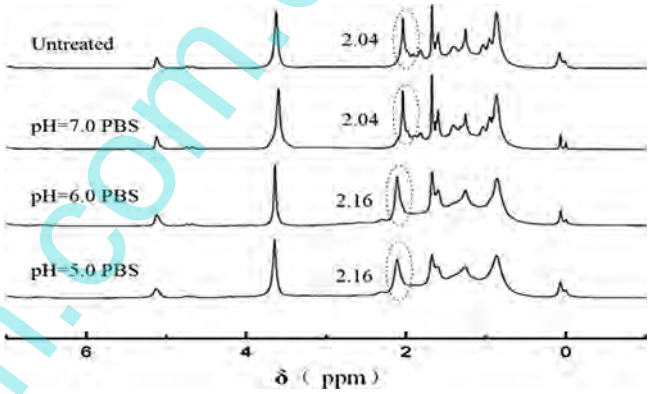

Fig. 10. ^{1}H NMR spectra of HMPSAs.

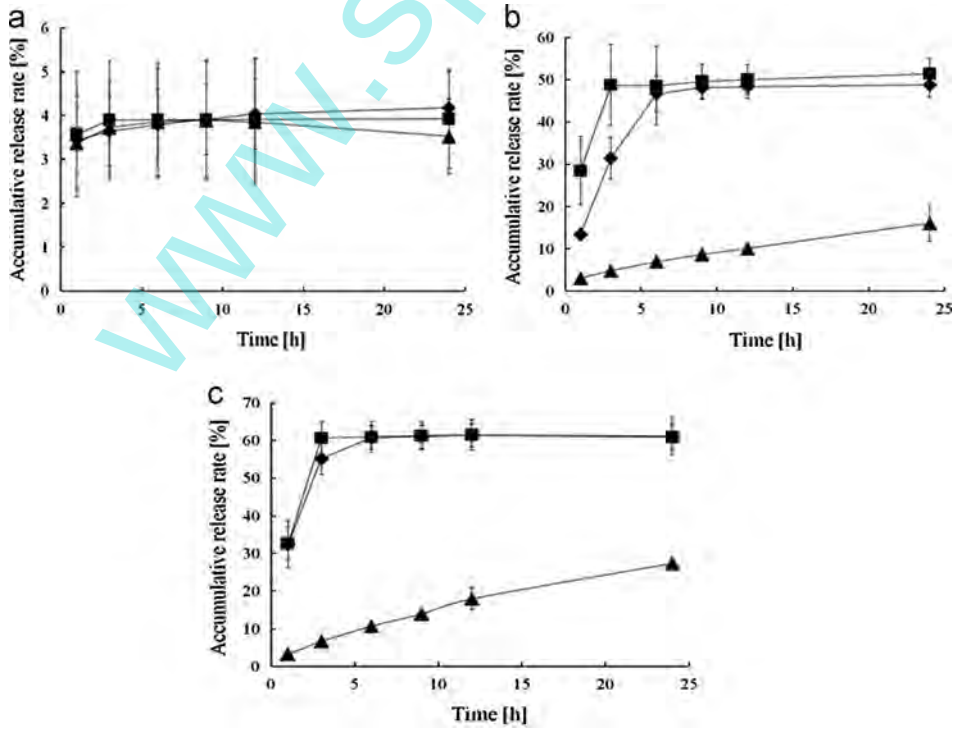

Fig. 9. Drug accumulative release curves of geniposide in pH-different conditions ((a) PEG:SEB=8:30, (b) PEG:SEB=13:30, (c) PEG:SEB=16:30, ▲pH=7.0, ◆pH=6.0, ■pH=5.0, n=3).

4. Conclusions

When mass ration of SIS: EPO was 1:1∼1:2, bi-continuous structure was formed. An appropriate amount of PEG, mineral oil and C_5 resin was added into the SEBs, amphiphilic HMPSAs can be fabricated. The amphiphilic HMPSAs exhibited good adhesive performance, continual release property of both hydrophilic and lipophilic drugs and more meliorative hygroscopicity compared to solely SIS-based HMPSAs. Due to the protonation of EPO, more rapid release and better hygroscopicity was evident in weakly acidic condition (pH=5.0∼6.0), further validating the SEB-based amphiphilic HMPSAs as a promising platform for TDDS.

Acknowledgments

The authors acknowledge the financial support of the Ministry of Science and Technology of China Twelfth 5-year Plan – The Study on the Novel Hot-melt Pressure Sensitive Adhesives Suitable for Chinese Medicine Patches (No. 2011ZX09501-001-02). The authors gratefully acknowledge the contribution of Tian-fu Wang and Zhong-fu Zhao in the revision of the manuscript.

References

[1] Wokovich AM, Prodduturi S, Doub WH, Hussain AS, Buhse LF. Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V 2006;64:1–8.
[2] Park Y-J, Joo H-S, Kim H-J, Lee Y-K. Adhesion and rheological properties of EVA-based hot-melt adhesives. International Journal of Adhesion and Adhesives 2006;26:571–6.
[3] Kim DJ, Kim HJ, Yoon GH. Effects of blending and coating methods on the performance of SIS (styrene-isoprene-styrene)-based pressure-sensitive adhesives. Journal of Adhesion Science and Technology 2004;18:1783–97.
[4] Webster I. Recent developments in pressure-sensitive adhesives for medical applications. International Journal of Adhesion and Adhesives 1997;17:69–73.
[5] Li H, Zeng X, Wu W. Epoxidation of styrene-isoprene-styrene block copolymer and its use for hot-melt pressure sensitive adhesives. Polymer-Plastics Technology and Engineering 2008;47:978–83.
[6] Hua L, Li Y, Wang Q, Hu Y, Zhao Z. Fabrication of amphiphilic hot-melt pressure sensitive adhesives for transdermal drug delivery. Journal of Adhesion Science and Technology 2012;26:1109–22.
[7] Sridevi S, Diwan PV. Optimized transdermal delivery of ketoprofen using pH and hydroxypropyl-beta-cyclodextrin as co-enhancers. European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V 2002;54:151–4.
[8] Vavrova K, Lorencova K, Klimentova J, Novotny J, Holy AN, Hrabalek A. Transdermal and dermal delivery of adefovir: effects of pH and permeation enhancers. European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V 2008;69:597–604.
[9] Sutinen R, Paronen P, Urtti A. Water-activated, pH-controlled patch in transdermal administration of timolol. I Preclinical tests. European Journal of Pharmaceutical Sciences: Official Journal of the European Federation for Pharmaceutical Sciences 2000;11:19–24.
[10] Wagner H, Kostka KH, Lehr CM, Schaefer UF. pH profiles in human skin: influence of two in vitro test systems for drug delivery testing. European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V 2003;55:57–65.
[11] Leopold CS, Eikeler D. Eudragit E. as coating material for the pH-controlled drug release in the topical treatment of inflammatory bowel disease (IBD). Journal of Drug Targeting 1998;6:85–94.
[12] Mark JE. Polymer data handbook. New York: Oxford University Press; 2009.
[13] Sarode AL, Sandhu H, Shah N, Malick W, Zia H. Hot melt extrusion (HME) for amorphous solid dispersions: predictive tools for processing and impact of drug-polymer interactions on supersaturation. European Journal of Pharmaceutical Sciences: Official Journal of the European Federation for Pharmaceutical Sciences 2012;48:371–84.
[14] Gardlund ZG. Properties and morphology of poly (methyl methacrylate)/bisphenol a polycarbonate blends, polymer blends and composites in multiphase systems. Advances in Chemistry Series 1984;206:129–48.
[15] Ide J, Nägele A, Ewald S. Eudragit® application guidelines, parsippany. NJ: Degussa Corporation; 2007.