Drug Development and Industrial Pharmacy, 2009; 35(6): 704–711

informa
healthcare

ORIGINAL ARTICLE

Preparation and characterization of PEG-modified polyurethane pressure-sensitive adhesives for transdermal drug delivery

Xuemei Chen[1,2], Wei Liu[2], Yanbing Zhao[3], Lingyu Jiang[2], Huibi Xu[3] and Xiangliang Yang[2]

[1]*School of Chemical Engineering and Materials, Huangshi Institute of Technology, Huangshi, China,* [2]*College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan, China and* [3]*Department of Chemistry, Huazhong University of Science and Technology, Wuhan, China*

Abstract

Background: The purpose of this work was to develop novel pressure-sensitive adhesives (PSAs) for transdermal drug-delivery systems (TDDS) with proper adhesive properties, hydrophilicity, biocompatibility and high drug loading. *Method*: Polyethyleneglycol-modified polyurethane PSAs (PEG-PU-PSAs) were synthesized by prepolymerization method with PEG-modified co-polyether and hexamethylene diisocyanate. The effects of reaction temperature, catalyst, ratios of NCO/OH, co-polyether composition, and chain extender were investigated. Drug loading was studied by using thiamazole (hydrophilic drug), diclofenac sodium (slightly hydrophilic drug), and ibuprofen (lipophilic drug) as model drugs. In vitro drug-release kinetics obtained with Franz diffusion cell and dialysis membrane. *Results*: The results showed that when reaction temperature at 80°C, weight percentage of stannous octoate as catalyst at 0.05%, ratio of NCO/OH at 2.0–2.2, ratio of PEG/polypropylene glycol (PPG)/polytetramethylene ether glycol (PTMG) at 30/25–30/50–55, and weight percentage of glycol as chain extender at 4.5%, PEGPU-PSAs synthesized performed well on adhesive properties. Actually, PEG on the main chain of the PU could improve the hydrophilicity of PSAs, whereas PPG and PTMG could offer proper adhesive properties. Skin compatibility test on volunteers indicated that PEG-PU-PSAs would not cause any skin irritations. All the model drugs had excellent stabilizations in PEG-PU-PSAs. In vitro drug-release kinetics demonstrated that the drug release depended on drug-loading level and solubility of the drug. *Conclusion*: These experimental results indicated that PEG-PU-PSAs have good potential for applications in TDDS.

Key words: *Co-polyether; drug loading; hydrophilic pressure-sensitive adhesives; in vitro drug release kinetics; polyurethane; PEG-modified; transdermal drug-delivery systems*

Introduction

Transdermal drug-delivery systems (TDDS) have drawn significant attentions during the last decades. Pressure-sensitive adhesives (PSAs) are one critical component in TDDS, which have great influences on the function of TDDS[1]. Three types of PSAs have been commonly used in TDDS: polyisobutylene (PIB), polysiloxane (silicone), and polyacrylate (acrylics) copolymers[2–4]. However, all these traditional PSAs have always been criticized for their defects. Because of their highly paraffinic and non-polar nature, PIB-based PSAs are only soluble in typical aliphatic and aromatic hydrocarbon solvents, which allow them to be only used in drugs with low-solubility parameter and low polarity. The structure of the close and unstrained molecular packing leads to the low permeability of PIB-based PSAs. Skin irritations such as erythema and edema would probably happen after using. Compared with PIB-based PSAs, silicone PSAs have better permeability. Their applications in various medical devices and their chemical and physiological inertness have been widely described in publications. However, because of their low duration of perspiration, skin irritations will also be induced occasionally. And silicone PSAs do not have

Address for correspondence: Dr. Wei Liu, College of Life Science and Technology, Huazhong University of Science and Technology, Luoyu Road 1037, Wuhan, 430074 China. Tel: +86 27 87792147, Fax: +86 27 87794517. E-mail: wliu@mail.hust.edu.cn

(Received 27 Mar 2008; accepted 28 Sep 2008)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.1080/03639040802512235

expected adhesive properties. Acrylic PSAs are produced by copolymerization of acrylic esters, acrylic acid, and other functional monomers and have significant improvements in both permeability and adhesive properties. But acrylic PSAs do not have expected biocompatibility and will probably cause skin reactions, as they are highly hydrophobic and might have residual monomers[5].

In general, traditional hydrophobic PSAs have some faults as follows: Firstly, it is painful peel off, even causing trauma to the wearer. Secondly, their repeated sticking property, moisture permeability, and biocompatibility are not good enough as expected. Thirdly, the kinds of drugs that are capable of these PSAs are limited and their drug loadings are low.

Recently, it has drawn tremendous attentions on how to develop PSAs with proper adhesive properties, better biocompatibility, and a wide range of drugs at high drug-loading level. To achieve these objectives, two approaches have been used[1,6,7]. One approach is to physically or chemically modify the traditional PSAs that have been used. The other is to develop new polymers, including hydrogels, hydrophilic polymers, and polyurethanes (PU).

PU are polymeric products of diols/polyols and diisocyanates/polyisocyanates. They are composed of 'hard' and 'soft' monomers or segments. The soft monomers yield a low glass-transition temperature polymer such as polyether, polyester, and polyolefin. The hard monomer is one that would give rise to a polymer with a high glass-transition temperature such as diisocyanates and the chain extender[8]. PU-PSAs with expected properties could be prepared by controlling the ratio of two monomers[9]. The application of traditional PU-PSAs for TDDS is limited for some reasons such as low moisture permeability, adhesive properties, and drug loading[10,11].

In this work, polyethyleneglycol (PEG)-PU-PSAs were synthesized by prepolymerization method with PEG-modified co-polyether and diisocyanate. PEG-modified method was supposed to be more available for developing a novel PSA for TDDS with proper adhesive properties, hydrophilicity, biocompatibility, and high drug loading. Then, the characterization of PEG-PU-PSAs such as adhesive properties, hydrophilicity, and skin compatibility was investigated. Drug loading and in vitro release kinetics of PEG-PU-PSAs was studied by using thiamazole (Mw = 114.16), diclofenac sodium (Mw = 318.13), and ibuprofen (Mw = 206.28) as model drugs.

Experimental

Materials

Hexamethylene diisocyanate (HDI) was purchased from Nippon Polyurethane Industry Co., Ltd. (Tokyo, Japan), PEG-2000 from Shenzhen Huada chemistry Company (Shenzhen, China), and polypropylene glycol (PPG-2000) from Jiangsu Hai'an Petrochemicals Company (Nantong, China), polytetramethylene ether glycol (PTMG-2000) from Mitsubishi Chemical Co., Ltd. (Tokyo, Japan). Stannous octoate was obtained from Aldrich (St. Louis, MO, USA). Butanone, glycol, glycerol, and 1,4-butanediol was supplied by Shanghai Chemical Company (Shanghai, China). Thiamazole was purchased from Beijing Tongjida Pharmacy Company (Beijing, China), diclofenac sodium from Wuhan Yuancheng Chemical Company (Wuhan, China), and ibuprofen from Wuhan Hezhong Chemical Company (Wuhan, China). Other reagents were of analytical grade. Distilled water was produced in this laboratory.

Methods

Synthesis of PEG-PU-PSAs

PU was synthesized based on prepolymerization method developed by Yilgor et al.[12] with modifications. PU product was obtained by adding the chain extender to the prepolymer of isocyanate. Reaction formulations of prepolymerization and chain-extender reaction were shown in Figure 1.

Briefly, PEG-2000, PPG-2000, and PTMG-2000 were mixed in a 500-mL three-neck flask, and heated at 120°C under vacuum for 4–6 hours to remove water. After cooling down to 60°C, the mixture of HDI and butanone was added in the flask. Then, stannous octoate, as a catalyst, was added to the reaction mixture. The reaction mixture was heated at 65°C, 75°C, 80°C, and 85°C, respectively, under nitrogen atmosphere to carry out prepolymerization. After prepolymerization, the reaction system was cooled to 60°C and fed with chain extender to carry out chain-extender reaction. When the reaction was finished, the final product was obtained after evaporation under vacuum at 90°C for 24 hours to remove the residual organic solvent.

Measurement of NCO content in prepolymer

The NCO content in prepolymer was measured using a method that was previously reported[13]. The sample was divided into two parts equally. One was dried in an oven to obtain solid weight (m_p). The other part was put into a 50-mL conical flask, added with 20 mL of 0.2 M dibutylamine solution in butanone for 30 minutes. Adding one or two drops of bromcresol blue as an indicator, the content would be measured by titration using 0.1 M hydrochloric acid. At the termination, the color of the mixture would turn to flavovirens. The NCO content (%) in prepolymer was calculated as follows:

$$NCO\% = \frac{(V_0 - V_s) \times C \times 42}{1000 m_p} \times 100\%,$$

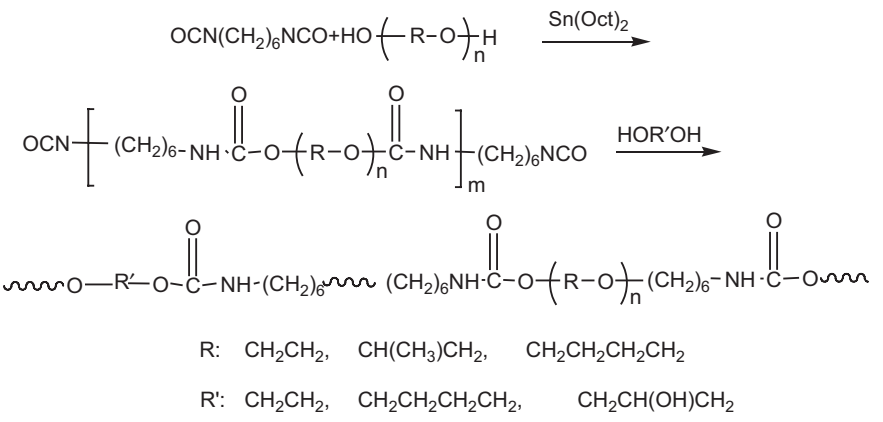

Figure 1. Reaction formulations of pre-polymerization and chain-extender reaction.

where V_0 is the volume of hydrochloric acid consumed by the blank (mL), V_S is the volume of hydrochloric acid consumed by the sample (mL), C is the concentration of hydrochloric acid (mol/L), m_p is the weight of the sample, the molecular weight (Mw) of NCO is 42. Three measurements were taken to get an average value.

Fourier transform infrared and gel permeation chromatography measurement

Fourier transform infrared (FTIR) spectrum of PEG-PU-PSAs was obtained with EQUINOX-55 spectrometer (Germany). Thirty-two scans were collected for each sample at a resolution of 2 cm^{-1} over the wave number region 4000–400 cm^{-1}.

Mw and polydispersity (Mw/Mn) of PEG-PU-PSAs were determined by gel permeation chromatography (GPC) system on a Waters system comprising a U6K injector, a 510 high-performance liquid chromatography (HPLC) solvent delivery system, an R401 differential refractometer, and a Maxima 820 control system. Two Waters 7.8 mm × 30 cm Ultrastyragel linear columns, in series, packed with 1×10^4 and 1×10^9. A particles of crosslinked styrene–divinylbenzene copolymer were utilized for the analysis. The eluting solvent was HPLC grade tetrahydrofuran (THF) at a flow rate of 0.7 mL/min. The retention times were calibrated against known monodisperse polystyrene standards: 47,500; 18,700; 5120, and 2200 whose Mw/Mn are less than 1.09.

Adhesive properties

Adhesive properties of PSAs for TDDS consisted of tack, holding power, 180° peel strength, and repeat peel-stick property. Tack test (oblique plane by rolling ball), holding power test, and 180° peel strength test were in accordance with GB4852-84, GB4851-84, and GB2792-81 of China Pharmacopoeia Commission (2005 Edition)[14]. Repeat peel-stick property was determined as follows: PSAs sample was stuck and peeled continuously on a clean stainless steel plate for 50 times. Then, 180° peel strength of the sample was measured. The decreasing percent of 180° peel strength compared with original was the standard of repeat peel-stick property. The lower the decreasing percent of 180° peel strength, the better the repeat peel-stick property was.

Water absorption rate

PEG-PU-PSAs sample was pressed with stainless steel applicator to give 1.5 ± 0.2-mm thickness film. After drying under reduced pressure, the film was weighed precisely and recorded as G_1. Dry film was put into distilled water for 2 hours. Then, the film was weighed precisely and recorded as G_2 after its surface water had been removed. Water absorption rate (Q) of the sample was calculated as follows:

$$Q(\%) = (G_2 - G_1)/G_1 \times 100\%.$$

Moisture permeability

Adding 100 mL distilled water to a 150-mL beaker, the total mass was recorded as W_1. The beaker with water sealed by PEG-PU-PSAs film (1.5 ± 0.2 mm thickness) was put into a thermotank at 37°C for 24 hours. After removing the PSAs film, the total mass of the beaker and remaining water was recorded as W_2. The moisture permeability rate (P, g/m^2/h) was estimated as follows:

$$P = \frac{W_1 - W_2}{24 \times S},$$

where S is the area of the cross section of the beaker.

Skin compatibility

PEG-PU-PSAs were coated onto nonwoven fabrics to give the patch of 6×6 cm^2 without drug. The patch samples were adhered on the arms of volunteers comprising six men and six women. The skin compatibility was judged after 48 hours according to the degree of the skin reaction including skin irritation and skin sensitization.

Drug-loading profile

PEG-PU-PSAs patches loaded with different drugs were prepared. Liquid PEG-PU-PSAs synthesized were cooled down and added with drugs. The mixture was evaporated under reduced pressure subsequently to remove the residual organic solvents. Then they were compressed with stainless steel applicator directly onto the nonwoven fabrics to give drug-loaded PEG-PU-PSAs patches. The appearance and adhesive properties, including tack, holding power, and 180° peel strength, were studied after one week at room temperature. Compared to those of blank patches, the differences were recorded to evaluate the drug loading of PEG-PU-PSAs patches. Drug extraction procedure was not involved in this research.

In vitro drug release kinetics

In vitro drug release kinetics was studied as described previously[14]. The improved Franz diffusion cell and the dialysis membrane were used in the research. The dialysis membrane was soaked in isopropyl myristate (IPM) for one night to simulate lipoid in cuticle before being used.

The modified Franz diffusion cell consisted of a donor cell and a receptor cell. The temperature was maintained at 37°C by circulating constant temperature water through the outer jacket of the receptor cell. The surface area of the receptor cell opening was 2.80 cm^2 and the cell volume was 7.0 mL. The dialysis membrane (Mw cutoff 6000) was mounted between the donor and the receptor cells and fastened with a rigid clamp. Each PEG-PU-PSAs patch was covered on the dialysis membrane facing the donor cell. After that, the receptor cell was filled with isotonic sodium chloride solution containing 30% (v/v) ethanol and was stirred by magnetic stirrer to keep them mixed well. At each predetermined time intervals, which were 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 30.0, 38.0, and 48.0 hours, 500 µL of sample solution was taken from the receptor cell for analysis and refilled with the same volume of the fresh receptor solution. Released drugs were then analyzed by UV-2102 PC UV spectroscopy (China) to determine the percentage of drug release. The UV-measured wavelength was 252 nm for thiamazole, 263 nm for ibuprofen, and 276 nm for diclofenac sodium, respectively. The assay was linear in the concentration range of 1.13–18.08 µg/mL for thiamazole (r^2 = 0.9989), 0.67–8.43 µg/mL for ibuprofen (r^2 = 0.9965), and 2.04–24.48 µg/mL for diclofenac sodium (r^2 = 0.9998), respectively. The method is simple, accurate, and reproducible.

Results and discussion

Characterization of PEG-PU-PSAs

As the major component of 'hard' segment, diisocyanate gave significant effect on adhesive properties of PU-PSAs. In our study, PU-PSAs were prepared using different types of diisocyanate as toluene diisocyanate (TDI), isophorone diisocyanate (IPDI), and HDI, respectively. Their chemical structural formulas were shown in Figure 2. It was found that the reaction rate was the fastest with TDI because of its inductive effect of aromatic ring, and the reaction rate was the slowest with IPDI because of its larger stereospecific blockade. However, PU-PSAs synthesized by TDI would turn to be toxic because of arylamine produced by hydrolysis[15,16]. On the basis of considerations above, HDI was employed in this work.

Figure 2 showed FTIR spectrum of PEG-PU-PSAs synthesized with HDI. The bands at 2940 and 2800 cm^{-1} were attributed to $-CH_3$ and $-CH_2$ stretching vibrations. The absorption peak at 1689 cm^{-1} was corresponding to the C=O stretch on the chain of PU. The band at 1536 cm^{-1} was due to secondary amine stretching mode. The absorption peak at 1250 cm^{-1} was corresponding to the C–O stretching vibrations of carbamate. And the band at 1109 cm^{-1} was attributed to the C–O–C dissymmetry stretching vibrations of co-polyether. The adsorption peak at 2300 cm^{-1}, NCO stretching did not appear in the spectrum, indicated that NCO was eliminated when the reaction proceeded.

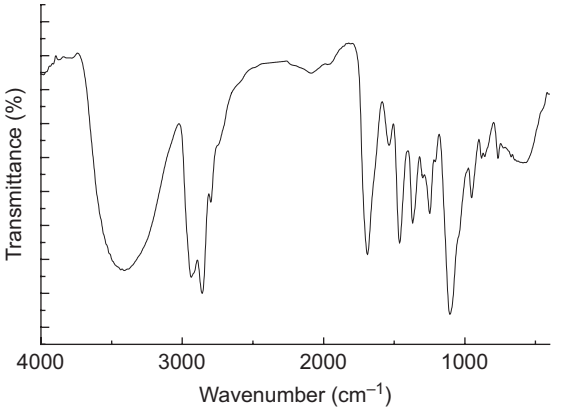

Figure 2. FTIR spectrum of PEG-PU-PSAs.

GPC measurement showed that Mw and Mw/Mn of PEG-PU-PSAs synthesized under different reaction conditions were between 29,500–46,000 and 1.84–2.36, respectively.

Effects of reaction temperature and catalyst on prepolymerization

Reaction temperature and catalyst played important roles in prepolymerization, which significantly affected prepolymer characteristics[17]. In this study, prepolymerization was taken under different temperatures (65°C, 75°C, 80°C, and 85°C, respectively), using stannous octoate as catalyst on different concentrations of 0.03–0.09%. When the content of residual NCO analyzed by titration was decreased to theoretical reaction termination, the reaction could be thought accomplished. And the reaction time was recorded. Effects of reaction temperature and catalyst on prepolymerization were shown in Figure 3.

Stannous octoate was approbated by FDA for using in medical and food industries. Because of its lower toxic and better catalysis activity, we chose it as the catalyst in our research[18]. As shown in Figure 4, the reaction would take shorter time with higher reaction temperature when using the same concentration of stannous octoate. And the reaction time would be decreased significantly followed the raise of the catalyst amount. However, when the catalyst amount was extremely high, as a result, the prepolymer synthesized had too broad Mw and the reaction rate was too fast, even out of control. On the basis of all the facts obtained, reaction temperature at 80°C and weight percentage of catalyst at 0.05% was employed.

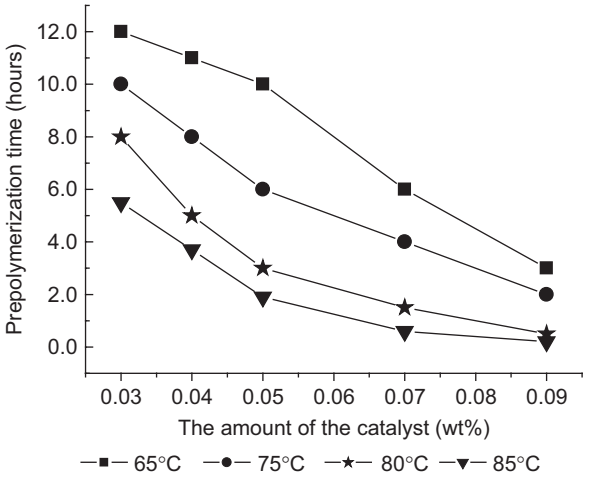

Figure 3. Effect of reaction temperature and catalyst on prepolymerization.

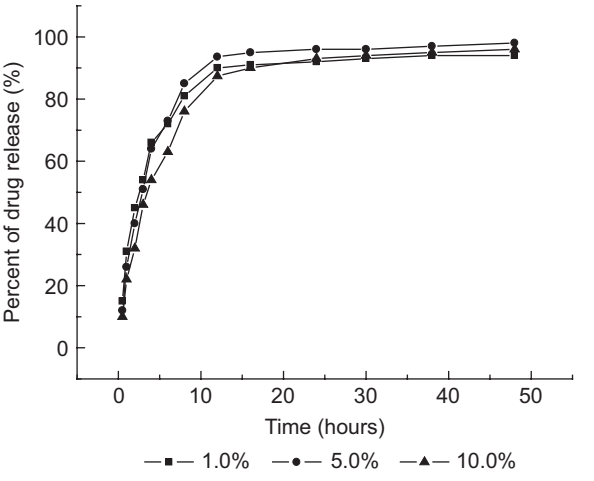

Figure 4. In vitro release kinetics of thiamazole from PEG-PU-PSAs.

Effect of ratios of NCO/OH on adhesive properties

PU was composed of 'hard' monomers such as diisocyanates and 'soft' monomers such as polyether. The desired adhesive property, including better adhesion to skin, longer wear time, even painless peel off, could be attained by controlling the ratio of NCO/OH.

Table 1 summarizes the effect of ratios of NCO/OH on adhesive properties of PEG-PU-PSAs (glycol was used as chain extender). The holding power, 180° peel strength, and repeat peel-stick property increased as the ratio of NCO/OH increased; however, the tack property decreased at the same time. The results suggested that adhesive properties of PEG-PU-PSAs would be the best when the ratio of NCO/OH was at 2.0–2.2.

Effect of ratios of PEG/PPG/PTMG on adhesive properties

Adhesive properties, particularly 180° peel strength and holding power, could be improved by the increase of PU crystallinity[9]. Crystallinity of PEG-PU-PSAs was highly affected by the ratio of PEG/PPG/PTMG. Table 2 summarizes the effect of ratios of PEG/PPG/PTMG on adhesive properties when the ratio of NCO/OH is at 2.2.

Table 1. Effect of ratios of NCO/OH on adhesive properties of PEG-PU-PSAs.

NCO/OH (mol/mol)	Tack (ball no.)	Holding power (hours)	180° peel strength (N/25 mm)	Repeat peel-stick property (%)
1.5	21	0.5	1.33	32.6
1.8	20	4.8	2.14	25.0
2.0	16	13.5	5.26	14.5
2.2	14	18.6	5.97	10.4
2.6	8	>24	7.64	17.2

Table 2. Effect of ratios of PEG/PPG/PTMG on adhesive properties of PEG-PU-PSAs.

	Compositon (mol/mol)			Adhesive property			
Number	PEG	PPG	PTMG	Tack (ball no.)	Holding power (hours)	180° peel strength (N/25 mm)	Repeat peel-stick property (%)
1	0	30	60	15	4.6	3.72	67.3
2	10	25	50	19	9.5	4.30	36.5
3	20	25	50	16	13.7	4.95	16.0
4	30	25	50	14	19.4	5.73	12.9
5	30	10	50	10	21.0	6.04	15.1
6	30	20	50	13	16.2	5.15	10.5
7	30	30	55	16	12.8	4.80	18.6
8	30	30	65	11	16.5	5.43	27.4

Table 2 indicated that the holding power, 180° peel strength, and repeat peel-stick property increased, but the tack came down, as the amount of PEG increased. When the amount of PPG increased, the tack improved while the holding power and the 180° peel strength came down, but the repeat peel-stick property was no more affected. As the amount of PTMG rises, there would be the same changes of the adhesive properties such as the effect induced by the increase of PEG. But if it increased to extremely high level, the repeat peel-stick property would be decreased.

Because PEG and PTMG had regular constructions and sound crystallizations, the adhesive properties especially the holding power and 180° peel strength would elevate remarkably as they are increased. On the other hand, the rise in the amount of PPG would enhance the tack, whereas the other adhesive properties would decrease. It is because PTMG had one more branch methyl, which would enlarge the stereospecific blockade of PEG-PU. Above these values, it could be conducted that the ratio of PEG/PPG/PTMG between 30/25–30/50 and 55 was acceptable.

Effect of chain extender on adhesive properties

Chain extender, as 'hard' monomers in PU, with crosslink of prepolymers to enhance Mw as its function, had significant influence on adhesive properties of PSAs[19]. It is also well known that reaction would be so fast that it is hard to control with diamine chain extenders. In addition, PEG-PU-PSAs obtained were too hard and their adhesive properties were in poor conditions. Compared with these, it used polyhydroxy compound as chain extenders. Table 3 summarizes the adhesive properties of PEG-PU-PSAs synthesized with three different polyhydroxy compounds as chain extenders, which was glycol, 1,4-butanediol, and glycerol. Use of glycerol as chain extender gave the lower tack property, higher 180° peel strength because of the high degree of crosslinking. On the contrary, use of 1,4-butanediol gave the higher tack, but the lower 180° peel strength and holding power. Moreover, PEG-PU-PSAs prepared with glycol could keep a balance among all aspects of adhesive properties. It was remarkable that adhesive properties of PEG-PU-PSAs with the amount of glycol at 4.5 wt% were much better than that obtained from the amount at 3.0 or 6.0 wt%. This might be due to the degree of crosslinking and Mw induced by the amount of glycol.

Table 3. Effect of chain extender on adhesive properties of PEG-PU-PSAs.

Chain extender	Amount (wt%)	Tack (ball no.)	Holding power (hours)	180° peel strength (N/25 mm)
Glycerol	4.5	8	17.4	5.05
1,4-butanediol	4.5	12	8.0	2.89
Glycol	3.0	17	10.2	3.50
	4.5	14	17.5	5.68
	6.0	11	22.6	4.25

Effect of ratios of PEG/PPG/PTMG on hydrophilicity

Table 4 showed the effect of the ratio of PEG/PPG/PTMG on water absorption rate and moisture permeability of PEG-PU-PSAs. It was nearly hydrophobic and nonpermeable without PEG containing in PU-PSAs.

Table 4. Effect of ratios of PEG/PPG/PTMG on water absorption rate and moisture permeability of PEG-PU-PSAs.

	Composition (mol/mol)			Characterization	
Number	PEG	PPG	PTMG	Q (%)	P (g/m^2/h)
1	0	30	60	0.7	1.3
2	10	25	50	8.6	14.9
3	20	25	50	17.0	22.6
4	30	25	50	27.9	26.8
5	30	10	50	33.2	29.5
6	30	20	50	26.3	23.7
7	30	30	55	21.7	19.4
8	30	30	65	18.4	17.6

The water absorption rate and moisture permeability improved significantly as PEG increased in the composition. However, there was no remarkable variance when the ratio of PPG or PTMG changed. It was confirmed that the hydrophilicity of PEG-PU-PSAs was controlled by the ratio of PEG. PEG was a linear hydrophilic polymer with numerous hydroxyl groups, had fewer methylene than PTMG, which made PEG form hydrogen bonds much easier with water to improve the hydrophilicity of PSAs. These findings strongly supported ideas that PEG-PU-PSAs had excellent hydrophilicity and had a bright future for applications in TDDS.

Furthermore, the chain extender also gave some effects on hydrophilicity. For example, PEG-PU-PSAs synthesized with glycol had better hydrophilicity than those synthesized with 1,4-butanediol. This might be due to the chain length and other properties of the chain extender.

Skin compatibility

Skin compatibility test of PEG-PU-PSAs showed that none of the twelve volunteers had visible skin reaction including abnormal reactions, skin irritations, and skin sensitizations during 48 hours with PEG-PU-PSAs patches adhered on their arms. Furthermore, the PEG-PU-PSAs patches could be removed less painfully, leaving no sticky residue. On the contrary, traditional hydrophobic PSAs could not absorb or penetrate the sweat because of their low hydrophilicity and moisture permeability, which would cause skin irritations and skin sensitizations. These results illustrated that PEG-PU-PSAs had excellent skin compatibility, which had overcome those faults of traditional hydrophobic PSAs.

Drug-loading profile

PU is a polymer with extraordinary high stabilization in physical and chemical characterization, and it could be stored at room temperature for a very long time[20]. Because there were both hydrophilic segments and lipophilic segments in PEG-modified PU (PEG-PU), it would enhance PSAs with better compatibility and stabilization with a wider range of drug at higher loading level. The adhesive properties of different drug-loaded PEG-PU-PSAs are summarized in Table 5.

The results showed that the adhesive properties of PSAs had no significant decrease with thiamazole (hydrophilic drug) and diclofenac sodium (slightly hydrophilic drug) loaded. Particularly, holding power and 180° peel strength had been enhanced with thiamazole loaded, which might be due to the increase of crystallization of PEG-PU-PSAs. In contrast, ibuprofen, a lipophilic drug, showed remarkable decrease on the adhesive properties. And the adhesive properties came down when drug loading increased. However, it still could be applied for TDDS when the loading level of ibuprofen was below 3.0 wt%.

Table 5. Adhesive properties of PEG-PU-PSAs loading different drug.

		Adhesive properties		
Drugs	Drug loading (wt%)	Tack (ball no.)	Holding power (hours)	180° peel strength (N/25 mm)
Blank	0	14	17.5	5.68
Thiamazole	1.0	14	17.8	5.83
	5.0	14	18.6	5.75
	10.0	13	18.0	5.37
Diclofenac	1.0	13	16.2	5.54
sodium	5.0	11	13.7	5.06
	10.0	10	8.5	4.47
Ibuprofen	1.0	12	13.6	5.21
	3.0	10	9.2	4.32
	6.0	7	2.4	2.85

In vitro drug release kinetics

In vitro drug release kinetics of PEG-PU-PSAs loading different drugs is shown in Figures 4–6. The drug release behavior from PEG-PU-PSAs exhibited a biphasic pattern, burst drug release, and sustained drug release. For transdermal application, both burst drug release and sustained drug release were of interest[21]. Burst release could be useful for improving the penetration of drug, whereas sustained release would be beneficial for drug with irritating effect at high concentration and would supply the skin over a prolonged period with active compound[22].

Figure 4 indicated that the release kinetics of thiamazole with different loading level, up to 90% drug released from PSAs within 12 hours and nearly 100% released at 48 hours. It suggested that thiamazole could

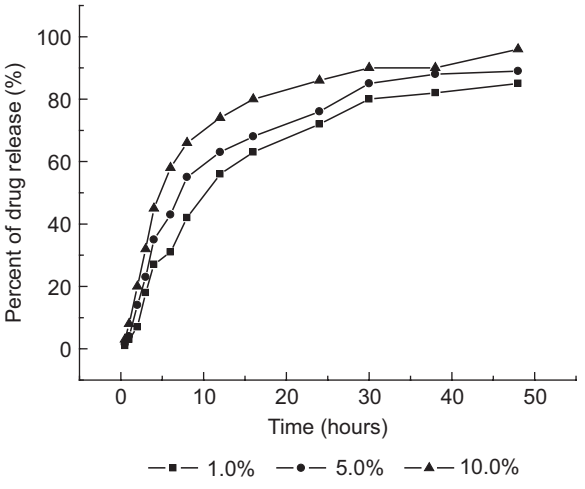

Figure 5. In vitro release kinetics of diclofenac sodium from PEG-PU-PSAs.

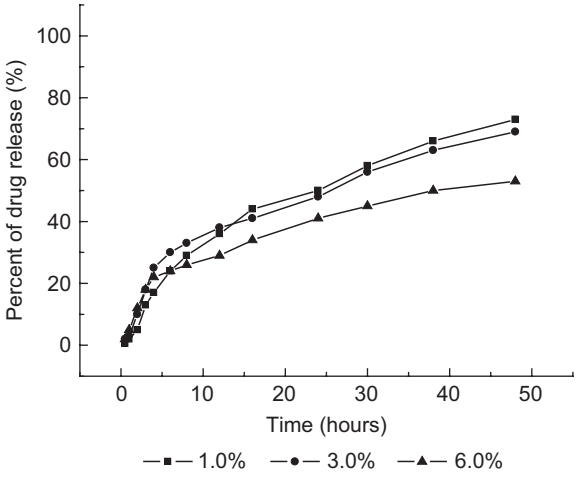

Figure 6. In vitro release kinetics of ibuprofen from PEG-PU-PSAs.

be moved easily in the hydrophilic polymer because of its high solubility. Figure 5 shows diclofenac sodium released from PSAs up to 68–89% within 24 hours. The release profile of diclofenac sodium was affected obviously with loading level: the higher the drug loading, the faster the drug released. Figure 6 shows that ibuprofen released from PSAs was much slower, with only 37–49% within 24 hours. These might be due to the low solubility of ibuprofen, which made ibuprofen nearly saturated and decreased its release from PEG-PU-PSAs.

Conclusions

Hydrophilic PEG-PU-PSAs for TDDS were studied in this article. According to the prior publications, traditional hydrophobic PSAs have many defects such as low repeating sticking property, low moisture permeability, low biocompatibility, and low drug-loading level. Especially, they were painful to peel off, even causing trauma to the wearer. Compared with those traditional PSAs for TDDS, PEG-PU-PSAs were significantly developed with improved hydrophilicity, adhesive properties, and biocompatibility. More detailed studies showed that PEG-PU-PSAs had better compatibility with a wider range of drugs at higher drug-loading level. In vitro drug release kinetics exhibited a biphasic pattern that is a benefit for transdermal drug delivery. All these results answer the hypothesis that PEG could improve the characters of PSAs. And they indicated that PEG-PU-PSAs have good potential for applications in TDDS.

Acknowledgments

This work was supported financially by the National Key Technology R&D Program (2001BA310A) of China and Key Technology R&D Program of Hubei Province of China (No. 2006AA304A07).

Declaration of interest: The authors report no conflicts of interest.

References

1. Tan SH, Pfister RW. (1999). Pressure-sensitive adhesives for transdermal drug delivery systems. PSTT, 2:60–9.
2. Kenney JF, Haddock TH, Sun RL. (1992). Medical-grade acrylic adhesives for skin contact. J Appl Polym Sci, 45:355–61.
3. Laureau C, Vicente M, Barandiaran MJ. (2001). Effect of the composition profile of 2-ethyl hexyl acrylate/methyl methacrylate latex particles on adhesion. J Appl Polym Sci, 81:1258–65.
4. Thomas BJ, Finnin BC. (2004). The transdermal revolution. Drug Discov Today, 16:697–703.
5. Yang O, Shen J. (2002). Formulations based on acrylic latex and polyurethane dispersion created for graphic labels and tapes. Adhe Age, 45(3):22–4.
6. Chivers RA. (2001). Easy removal of pressure sensitive adhesives for skin applications. Int J Adhes Adhes, 21:381–8.
7. Hopp MS. (2002). Developing custom adhesive systems for transdermal drug delivery products. Pharmaceutical Tech, 26:30–6.
8. Venkatraman S, Gale R. (1998). Skin adhesives and skin adhesion. 1. Transdermal drug delivery systems. Biomaterials, 19:1119–36.
9. Gnanarajan PT, Iyer PN, Nasar SA. (2002). Preparation and properties of poly (urethane-imide)s derived from amine-blocked-polyurethane prepolymer and pyromellitic dianhydride. Eur Polym J, 38:487–95.
10. Chang T, Kuo S, Chen R. (1999). Polyurethane pressure-sensitive adhesives. United States Patent No. 5,952, 422.
11. Kinning DJ. (2001). Bulk, surface, and interfacial characterization of silicone-polyurea segmented copolymers. J Adhe, 75:1–26.
12. Yilgor I, Yilgor E. (1999). Hydrophilic polyurethaneurea membranes: Influence of soft block composition on the water vapor permeation rates. Polymer, 40:5575–81.
13. Xie F, Mou D. (2005). Synthesis of polyether-polyol type polyurethane elastomer by quasi-prepolymer method. J Chin Adhe. in China, 26:10–2.
14. China Pharmacopoeia Commission. (2005). China Pharmacopoeia, 2005 edition, Appendix: 78–9.
15. Venkateswarlu V, Manjunath K. (2004). Preparation, characterization and in vitro release kinetics of clozapine solid lipid nanoparticles. J Control Release, 95:627.
16. Tang WT, Labowb SR, Santerrea PJ. (2003). Isolation of methylene diamine and aqueous-soluble biodegradation products from polycarbonate-polyurethanes. Biomaterials, 24:2805–19.
17. Yang Z, Deng Y. (2003). Water-soluble/dispersible cationic pressure-sensitive adhesives. I. Adhesives from solution polymerization. J Appl Polym Sci, 90:1624–30.
18. Yamamoto M, Nakano F, Doi T, Moroishi Y. (2002). Synthesis and PSA performance study for novel acrylic and butyl acrylate block copolymers. Int J Adhes Adhes, 22:37–40.
19. Cilurzo F, Minghetti P, Casiraghi A, Tosi L, Pagani S, Montanari L. (2005). Polymethacrylates as crystallization inhibitors in monolayer transdermal patches containing ibuprofen. Eur J Pharm Biopharm, 60:61–6.
20. Czech Z. (2007). New generation of crosslinking agents based on multifunctional methylaziridines. Int J Adhes Adhes, 27:49–58.
21. Jenning V, Schafer-Korting M, Gohla S. (2000). Vitamin A-loaded solid lipid nanoparticles for topical use: Drug release properties. J Control Release, 66:115–26.
22. Hayashi T, Yamazaki T, Yamaguchi Y, Sugibayashi K, Morimoto Y. (1997). Release kinetics of indomethacin from pressure sensitive adhesive matrices. J Control Release, 43:213–21.