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Research Article

Development and Evaluation of α-Asarone Transdermal Patches Based on Hot-Melt Pressure-Sensitive Adhesives

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Abstract. A hot-melt, pressure-sensitive adhesive (HMPSA) based on styrene–isoprene–styrene was prepared, and its compatibility with various transdermal penetration enhancers was investigated. The effect of penetration enhancers on the adhesion properties of HMPSA was also studied. A drug-in-adhesive patch was formulated using α-asarone as a model drug, and penetration enhancers were screened by an *in vitro* transdermal study across excised pig skin. The pharmacokinetics in rabbits was also studied. The results show that HMPSA was miscible with most penetration enhancers (azone, menthol, isopropyl myristate, 1-methyl-pyrrolidinone, *N*,*N*-dimethylformamide, oleic acid), apart from propylene glycol. Penetration enhancers had a plasticizer-like effect that decreased the peel strength and shear strength of HMPSA. A combination of 1% oleic acid and 4% menthol had the highest *in vitro* penetration rate and was selected for patch preparation. The patch formulation was optimized by replacing some of the plasticizer by penetration enhancers to achieve good adhesion and effective transdermal flux. The final patch showed a high efficiency, with a relative bioavailability of 1,494%. This suggests that HMPSA may be a promising material for drug-delivery patches.

KEY WORDS: α-asarone; drug-in-adhesive patch; hot melt pressure sensitive adhesive; penetration enhancer; transdermal.

INTRODUCTION

Drug-in-adhesive (DIA) patches consist of a back-filling layer, a polymeric adhesive layer, and a non-sticking layer (1). A DIA is the simplest form of patch as the drug is directly loaded in a pressure-sensitive adhesive (PSA) in solubilized form. DIA patches can be produced using simple procedures, with reproducible quality, and the dose can be adjusted by cutting the patch to an appropriate size (2). When in contact with human skin, the drug is released from the transdermal patch at a controlled rate and diffuses into the skin.

PSA, a material that displays aggressive and permanent tack at room temperature and can be applied with very light pressure, is a critical component in DIA patches as it not only controls drug release but is expected to have good biocompatibility with skin (3). Traditionally, the process of coating PSAs on the support involves organic solvents, which are subsequently evaporated using a hot air dryer. However, the demand for low-cost and environmentally friendly adhesive products has led to recent growth in the field of hot melt PSAs (HMPSAs) (4). HMPSAs are composed of an elastomeric polymer, tackifying resins, plasticizers, fillers, and antioxidants in various amounts according to the properties desired. Styrene–isoprene–styrene tri-block copolymer (SIS) is the most common styrene-based block copolymer used for HMPSAs. Adhesive systems based on SIS can be formulated to provide aggressive tack, tailored peel adhesion and high cohesive strength (5). SIS-based PSA has been used to prepare transdermal patches as a solvent-type PSA (6,7). Our previous study found that SIS-based HMPSA is compatible with lipophilic drugs and can release drugs continuously (8). Recently, it was found that drug release from HMPSA is related to its cohesion, the structure of the polymer, and the plasticizer content in the formulation (9,10). These studies pioneered the use of SIS-based HMPSA in the field of transdermal drug delivery.

α-Asarone is one of the main functional ingredients in *Acorus gramineus* Soland. Its pharmacological effects include anti-hyperlipidemic, anti-inflammatory, and antioxidant activities (11). There are a number of products available in the market, such as oral preparations (e.g., tablets, capsules) and injections of α-asarone. However, oral administration of α-asarone induces poor bioavailability, which is only 2.75% and 5% for capsules and tablets, respectively (12), while invasive injection is not favored by patients. α-Asarone could be eliminated quickly with a biological half-life of about 2 h, and it needs to be administrated several times per day. Therefore, the development of non-invasive dosage forms with satisfactory bioavailability is critically needed. α-Asarone is a good candidate for transdermal administration because it has an appropriate pKa (2.86), molecular weight (208) and can be released rapidly from an HMPSA (8). In the present study, an HMPSA was prepared

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using SIS as a base material, and its miscibility with penetration enhancers was investigated. The penetration enhancers were screened with an *in vitro* transdermal study using α-asarone as a model drug, and a DIA patch containing α-asarone was constructed with an optimized formulation. The pharmacokinetics in rabbits was also studied.

MATERIALS AND METHODS

Materials

α-Asarone was purchased from Yuancheng Technology (Wuhan, China). SIS-1161 was purchased from Kraton (Houston, TX, USA). C5 hydrogenate petroleum resin (C5RH) was a gift from Huifeng (Lanzhou, China). Lanoline, liquid paraffin (LPF), dibutyl phthalate (DHP), 2,6-ditertbutyl-p-cresol (DTBC), menthol (MEN), and oleic acid (OA) were purchased from Huadong (Hangzhou, China). Myristic acid isopropyl ester (IPM) was purchased from Sigma (St. Louis, MO, USA). Methanol was high-performance liquid chromatography (HPLC) grade and was purchased from Merck (Darmstadt, Germany).

Newborn pigs (9–10 days old, about 1.5 kg) and New Zealand white rabbits (male, 2.5–3.0 kg) were obtained from the Experimental Animal Center of Zhejiang University (Hangzhou, China). All the procedures and care administered to the animals had been approved by Experimental Animal Use Committee of Zhejiang University, and the animal experiments were conducted in full compliance with the Experimental Animal Regulations by the National Science and Technology Commission, China.

Preparation of HMPSA

The excipients (Table I) were placed in a flask and heated to 160–180°C in an oil bath under a nitrogen atmosphere and continuously stirred for 2 h. The backing layer, a piece of aluminum foil which laid on a hot plate at 100°C, was then coated quickly with the resultant mixture using a self-assembled film applicator with an average coating amount of 10 mg/cm^2. Then, the substrate was removed from the hot plate immediately. A piece of siliconized paper was used as a non-sticking layer to cover the patch while the adhesive was cooled down to room temperature.

Table I. Formulation of HMPSA

Excipient		Mass/g
Base material	SIS	100
Tackifying resin	C5RH	140
Plasticizer	LPF	40
	DHP	20
Hydrophilic adjustor	lanoline	20
Antioxidant	DTBC	2

SIS styrene–isoprene–styrene tri-block copolymer, *C5RH* C5 hydrogenate petroleum resin, *LPF* liquid paraffin, *DHP* dibutyl phthalate, *DTBC* 2,6-di-*tert*-butyl-*p*-cresol

Miscibility of HMPSAs with Penetration Enhancers

Penetration enhancers were added to the melted HMPSAs during the heating process at a mass ratio of 5%, under constant stirring. The mixture was then coated onto the backing substrate. The adhesive properties were measured to evaluate the miscibility of the HMPSAs and penetration enhancers.

Test of Adhesive Properties

The tackiness of the patches was determined by the rolling ball test carried on a tackiness tester (Geruite Analysis, Jinan, China). In brief, the patches were cut into 10-cm lengths and placed on a flat panel set an angle 30° from the horizontal. A series of steel balls with various diameters were rolled down the panel and over the patches after an initial acceleration length of 10 cm. The number of the largest ball retarded on the patches was recorded as the tackiness. The test was repeated three times.

The peel strength test was conducted by an auto stripping tester (Labthink, Jinan, China) measuring the force required to peel the patch away from a substrate. The patches were cut into 2.5-cm widths and applied onto a substrate (a stainless steel test panel) for 20 min. The patches were then peeled away at an angle of 180° at a speed of 10 mm/s. The peel adhesion was represented by the force required per unit width.

Shear strength was tested by applying the patches (1×1 cm) to a vertical stainless steel test panel. Twenty minutes after application, the test patch was subjected to a shear force via a given weight (50 g). The dwell times were recorded as the shear strength (1,13).

In Vitro Transdermal Study

Drug and penetration enhancers were added to the melted HMPSAs during the heating process, under constant stirring. The mixture was then coated onto the backing substrate. A piece of siliconized paper was used to cover the patch while the adhesive containing drug was cooled down to room temperature.

Skin was obtained from the back and abdomen of a 9- to 10-day-old pig using procedures approved by the Experimental Animal Use Committee of Zhejiang University. The skin was frozen at −80°C until use.

Vertical diffusion cells (diffusion area, 2.83 cm^2; volume of receiving chamber, 6.8 ml) were used for an *in vitro* percutaneous study. Saline containing 20% PEG-400 was used as the receptor medium. The patches were applied to the surfaces of the skin samples, and the experiment was performed at 37°C with stirring at 250 rpm. The receptor medium (1 ml) was sampled at predetermined times up to 24 h, with replenishment by equal volumes of fresh medium. The drug concentration in each sample was determined by an HPLC-UV method with a Zorbax Eclipse XDB-C18 reversed phase chromatography column (250×4.6 mm, 5 μm stationary phase resin diameter, Agilent Technologies, Sent Clara, California, USA). The mobile phase was methanol/water (70:30), and the analysis was run under the following conditions. The column temperature was set at 40°C, the flow rate at 1.0 ml/min, and the detection wavelength at

257 nm. The method showed good linearity and precision over the range 1.6 to 200 μg·ml^{-1} (r=0.9999).

In Vivo Study

The *in vivo* study was performed with six male rabbits. One day before each experiment, the test skin area on the back of the animals was shaved without damaging the skin. The animals were then treated with the patches (120 cm^2, 1.5 mg α-asarone/cm^2), one patch per animal. The other group was given an oral dose of 180 mg α-asarone in a 1% carboxymethyl cellulose-Na suspension (10 ml). Blood samples were collected at predetermined time intervals, using heparin as an anticoagulant. Drug concentrations in plasma were determined by HPLC with fluorescence detection to enhance sensitivity. The HPLC conditions were as follows. The flow rate was set at 1.0 ml/min with a mobile phase of methanol/water (75:25) and a ZORBAX Eclipse XDB-C18 column as above, at excitation and emission wavelengths of 265 and 365 nm, respectively. The method was shown to have good linearity and precision over the range 0.01 to 1 μg·ml^{-1} (r=0.9998).

Statistical Analysis

Statistical analysis was performed using the ANOVA method. All data are presented as the mean value ± standard variation (SD).

RESULTS

Miscibility with Penetration Enhancers

HMPSA was miscible with most penetration enhancers, characterized by the appearance of slightly yellow, transparent

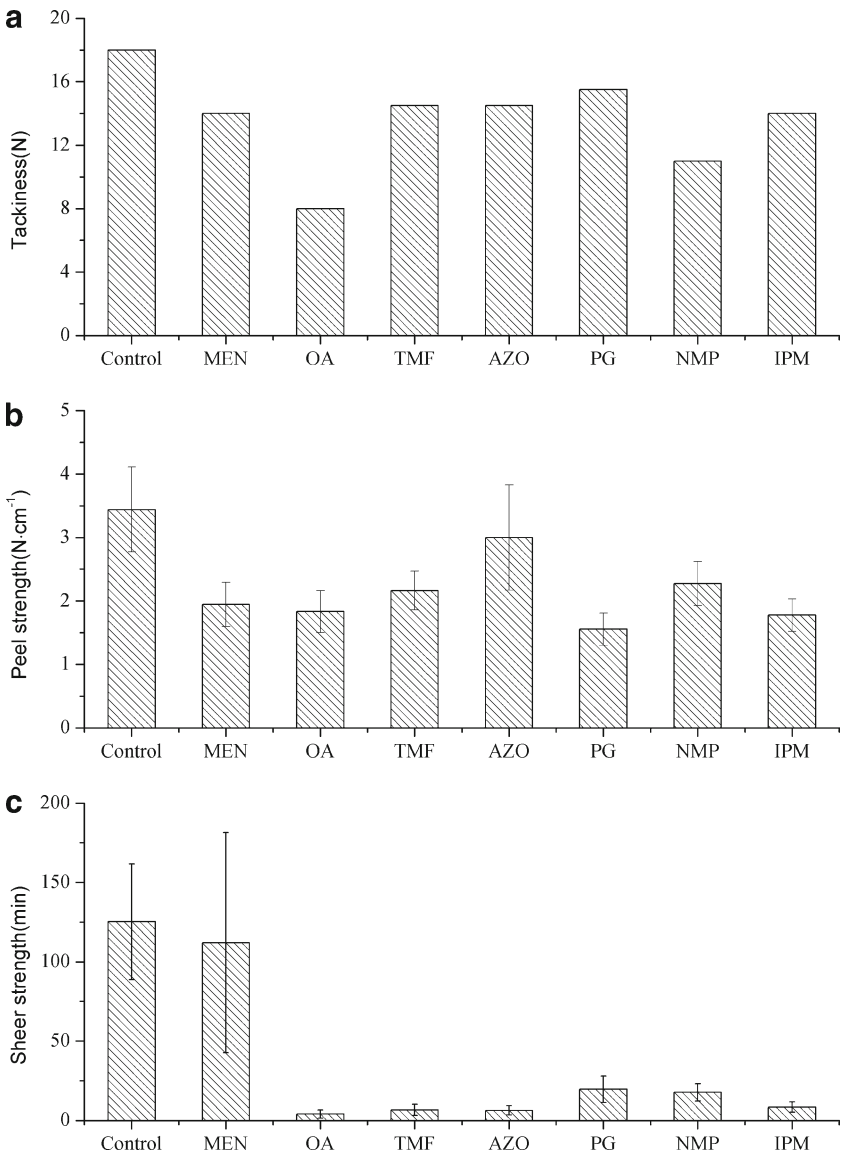

Fig. 1. Influence of penetration enhancers on adhesive properties of HMPSA. (n=3) **a** influence on tackiness, **b** influence on peel strength, **c** influence on sheer strength; *Control* no enhancer; *MEN* menthol, *OA* oleic acid, *DMF N,N*-dimethylformamide, *AZO* azone, *PG* propylene glycol, *NMP* 1-methyl-pyrrolidinone, *IPM* isopropyl myristate

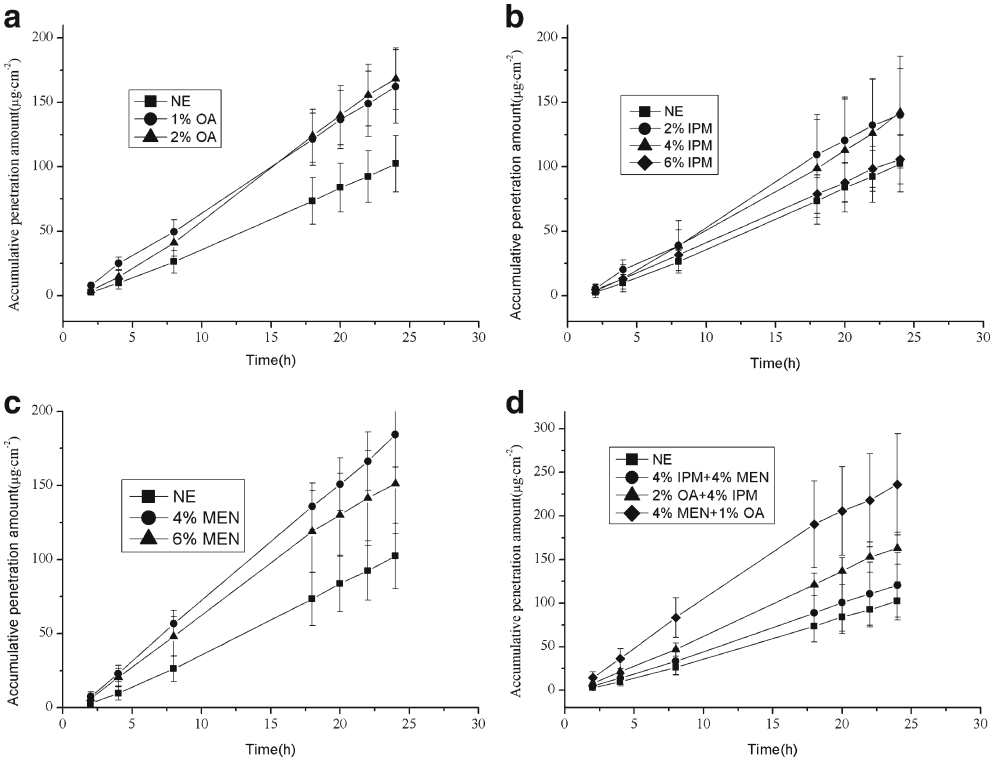

Fig. 2. *In vitro* permeation Profiles of the α-asarone patches prepared by HMPSA containing various penetration enhancers in pig skin (*NE* no enhancement, *OA* oleic acid, *IPM* isopropyl myristate, *MEN* menthol)

solids. The exception was propylene glycol (PG), for which the immiscibility of the HMPSA and PG mixture was indicated by the appearance of an opaque, white solid.

The adhesion properties of HMPSAs incorporating various penetration enhancers were investigated, and the results are shown in Fig. 1. The tackiness and peel strength of HMPSA were affected slightly by addition of various penetration enhancers. However, the shear strength of the HMPSA was substantially decreased by the penetration enhancers, which showed a similar effect as a plasticizer.

Table II. Transdermal Parameters of α-Asarone Patches Prepared by HMPSA Containing Various Penetration Enhancers (n=3)

	$Js/\mu g \cdot cm^{-2} \cdot h^{-1}$	SD	ER
NE	4.80	0.89	–
2% IPM	6.75	1.75	1.41
4% IPM	7.22	1.23	1.50
6% IPM	4.74	0.98	0.99
1% OA	7.09	1.19	1.48
2% OA	8.20	1.01	1.71
5% OA	6.84	1.56	1.42
4% MEN	8.07	1.26	1.68
6% MEN	6.76	1.32	1.41
2% OA+4% IPM	6.91	0.93	1.44
4% IPM+4% MEN	5.30	0.82	1.10
4% MEN+1% OA	9.62	2.20	2.00

NE no enhancement, *OA* oleic acid, *IPM* isopropyl myristate, *MEN* menthol, *Js* the flux, *SD* standard deviation, *ER* enhancement ratio

In Vitro Transdermal Study

The *in vitro* transdermal properties of HMPSA patches with various penetration enhancers were investigated. Transdermal efficiency was represented by the cumulative drug permeation per area, plotted as a function of time (Fig. 2). The steady transdermal flux was calculated from the slopes of regression functions in the linear curves (Table II). Compared with the control, all penetration enhancers tested enhanced drug permeation and combination of 4% MEN and 1% OA showed the highest transdermal flux.

Patch Formulation Optimization

Four percent MEN and 1% OA were selected as a synergistic combination of penetration enhancers for the α-asarone

Table III. Formulation of Patches

Excipient	P-1	P-2	P-3
SIS/g	100		
C5RH/g	140		
lanoline/g	20		
LPF/g	40	20	20
DHP/g	20	10	10
DTBC/g	2		
MEN	4%		
OA	1%		
α-asarone	10%	10%	15%

SIS styrene–isoprene–styrene tri-block copolymer, *C5RH* C5 hydrogenate petroleum resin, *LPF* liquid paraffin, *DHP* dibutyl phthalate, *DTBC* 2,6-di-*tert*-butyl-*p*-cresol, *MEN* menthol, *OA* oleic acid

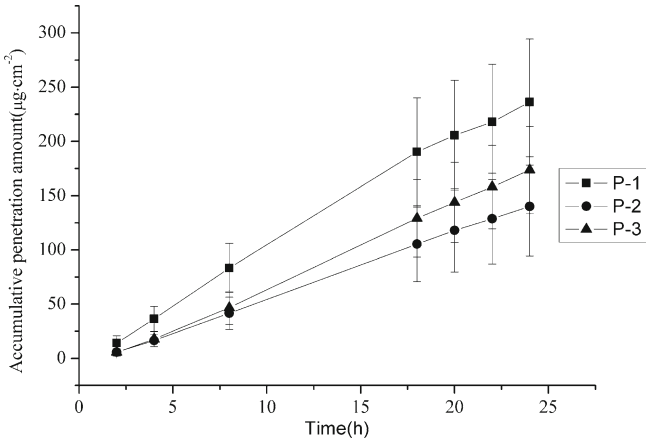

Fig. 3. Profiles of *in vitro* permeation from patches through pig skin (n=3)

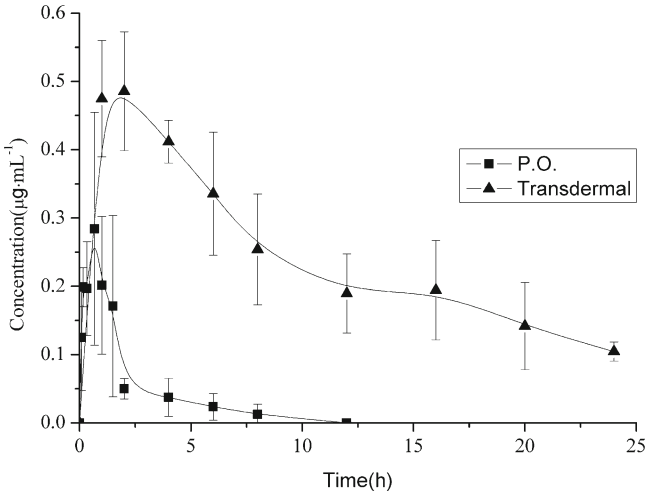

Fig. 4. Plasma concentration–time profiles after administration of α-asarone patch or suspension on rabbits. Each time point represents the mean ± SD (n=3)

patch because this combination resulted in the highest transdermal flux observed in the study. However, the shear strength of this formulation was low. We therefore conducted optimization of the formulation and designed several patches, as shown in Table III. The *in vitro* penetration and adhesion properties were studied, and the results are shown in Fig. 3 and Table IV. The P-2 and P-3 formulations displayed improved shear strength with decreasing plasticizer content, and the P-3 formulation was selected as the optimal formulation because it had superior adhesion properties and could deliver a suitable dose.

In Vivo Study

The P-3 formulation patches were used for *in vivo* assessment. The blood concentrations of α-asarone *vs* time are plotted in Fig. 4. The pharmacokinetic parameters were calculated by Thermo Kinetica software (version 4.4.1, Thermo Electron Corporation, Waltham, MA, US) and are listed in Table V. The area under the curve (AUC) of α-asarone for the P-3 patch was significantly increased compared with an oral dosage, and the relative bioavailability of the patch was 1,494%.

DISCUSSION

Solvent coating of patches involves heavy use of organic solvents, causing many problems, such as environmental pollution, energy wastage, and low production rates. In recent years, emulsion- and water-based PSAs have been widely investigated to eliminate the use of organic solvents, but a new problem also arises in that the drying processes become time-consuming (14,15). A promising solution to these problems may be the use of HMPSAs, which are coated in molten form, leading to significant cost savings, simplification of the process, and environmental friendliness. Although HMPSA techniques are widely used in tapes, cars, prints, and other products, few attempts have been made to incorporate drugs into HMPSAs. We previously reported that HMPSAs are compatible with lipophilic drugs, and drug release from them follows the Higuchi equation, therefore indicating that they are a promising material for patches (8).

HMPSAs are multi-component mixtures. In this study, the HMPSA composition was optimized as comprising SIS, C5 petroleum resin, lanoline, LPF, DHP, and DTBC. Thermoplastic elastomers such as styrene-based block copolymers have been widely used in PSAs because of their unique structures and processing advantages (16). For example, they flow at high temperatures and physically cross-link at low temperatures, thereby allowing the use of materials with low molecular weight to replace the traditional natural-rubber PSAs that function via physical entanglements. The isoprene segment is the noncrystalline zone of the triblock, while the styrene segment is the crystalline part. It was reported that drug release rate increased with a lower degree of crystallinity of PSA when SIS-1161 with a styrene segment ratio of 15% was used as a base material (17). Hydrogenate C5 petroleum resin was selected in our study as a tackifier because of its good tacking properties and faint color. LPF and DHP were selected as plasticizers. Because these components of the HMPSA are nonpolar and hydrophobic, lanoline was added to the PSA system to increase polarity. DTBC was used as an antioxidant to prevent oxidation of SIS, in which the double bonds become unstable at high temperature.

Table IV. Adhesion Properties and Transdermal Fluxes of Patches (n=3)

Formulation	Tackiness/N	Peel strength/ $N \cdot cm^{-1}$	Sheer strength/min	$Js/\mu g \cdot cm^{-2} \cdot h^{-1}$
P-1	12	2.39±0.54	66.3±44.8	9.62±2.20
P-2	13.5	2.17±0.17	>360	6.28±1.94
P-3	12	1.39±0.42	>360	8.10±1.40

Js the flux

Table V. Pharmacokinetic Parameters of the *In Vivo* Study (n=3)

Pharmacokinetic parameters	Oral	Transdermal
$Cmax/\mu g \cdot mL^{-1}$	0.2929±0.1607	0.4964±0.0763
Tmax/h	0.56±0.19	1.67±0.58
$AUC_{0\rightarrow t}/\mu g \cdot h \cdot mL^{-1}$	0.5259±0.2278	7.860±2.151
F	1,494%	

Cmax peak concentration, *Tmax* peak time, *AUC* bioavailability, *F* relative bioavailability of transdermal administration to oral

It is important for a transdermal HMPSA to be compatible with penetration enhancers. HMPSA was found to be compatible with the vast majority of penetration enhancers that are hydrophobic or amphipathic, but not with the hydrophilic PG. The various penetration enhancers showed similar effects on the adhesive properties of HMPSA, with slight reduction in the tackiness and peel strength, but significant loss in shear strength (a plasticizer-like action).

IPM and OA are widely used penetration enhancers and were reported to have good enhancing effect on transdermal of α-asarone. IPM is an aliphatic ester which is used as a safe PE in pharmaceutical products. IPM probably penetrates between the lipid bilayers of stratum corneum and disrupts the order and arrangement of lipid bilayers (18). OA was a kind of fatty acid which promotes penetration mainly through the enhancement of partitioning the drugs into the stratum corneum intercellular lipid domain (19). MEN is a common penetration enhancer used in traditional Chinese medicine. It is a lipophlic terpene which is considered to enhance lipophlic drug permeation through disrupting the stratum corneum bilayer lipids and improve drug diffusivity (20). IPM, OA, and MEN were selected as penetration enhancer of α-asarone patch. Often, percutaneous absorption rate can be enhanced by raising the concentration of a penetration enhancer. However, an excessive concentration of penetration enhancer can cause skin irritation and decrease transdermal flux because of drug retention in the patch (21). In the current study, excessive IPM and MEN had both produced lower percutaneous flux. Limitations with the use of a single penetration enhancer can be effectively overcome by the synergistic effect of combining multiple penetration enhancers. Several studies described the combination of two or more penetration enhancers for transdermal delivery (22–24). In this study, transdermal flux was significantly increased by combining 4% MEN and 1% OA, showing a twofold higher flux rate than the control group and demonstrating a synergistic effect on promoting α-asarone percutaneous absorption. It may due to the different penetration enhancement mechanism of MEN and OA. MEN and IPM had sheared the same mechanism that disrupting the stratum corneum lipid bilayer and the combination of 4% MEN and 4% IPM had even caused lower transdermal flux than single use.

To overcome the skin barrier and maintain an effective drug concentration in the blood, the amount of penetration enhancer in patches must be strategically selected. There is very limited capacity for incorporation of penetration enhancers with traditional PSAs in DIA patches. Large amounts of enhancer could cause a significant impact on the adhesive properties, for example, decreased peel strength and shear strength of PSA (25). The adhesive properties of HMPSA can be readily modified by altering the ratio of the excipients. As mentioned above, enhancers possess a plasticizer-like effect on the adhesive properties of HMPSA. In our study, the patch consisted by original formulation HMPSA and optimal penetration enhancer combination had poor shear strength. We thus applied the enhancers to partially substitute for the plasticizer in HMPSA. Our results show that the patch had acceptable adhesive properties, even with .a high loading of enhancer in HMPSA. Although the increasing shear strength could lower the drug release rate and thus decrease the transdermal flux, the penetrated drug amount could also achieve a therapeutic effect.

In vivo studies on rabbits demonstrated the promise of the HMPSA patch for transdermal delivery of α-asarone. The relative bioavailability of the HMPSA patch was 1,494% compared with an oral dose, while it was reported that the relative bioavailabilities of DIA patches prepared by Eudragit E PO and reservoir type patches were 426% and 951%, respectively (26). Furthermore, no skin irritation was observed after the transdermal experiments with HMPSA, demonstrating its biocompatibility.

CONCLUSIONS

An α-asarone DIA patch was successfully prepared using HMPSA in this study. The highest transdermal flux was achieved by combined use of 1% OA and 4% MEN. An *in vivo* study demonstrated improved bioavailability of the α-asarone patch. The results indicate that HMPSA is a promising material for patch preparation and that a DIA patch is an alternate route for α-asarone administration.

Declaration of interest The authors report no conflict of interest.

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