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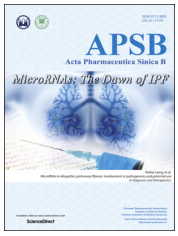

SHORT COMMUNICATION

Effect of isopropyl myristate on the viscoelasticity and drug release of a drug-in-adhesive transdermal patch containing blonanserin

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KEY WORDS

Isopropyl myristate;
Drug-in-adhesive patch;
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Blonanserin

Abstract The purpose of this study was to investigate the effect of isopropyl myristate (IPM), a penetration enhancer, on the viscoelasticity and drug release of a drug-in-adhesive transdermal patch containing blonanserin. The patches were prepared with DURO-TAK® 87-2287 as a pressure-sensitive adhesive (PSA) containing 5% (*w*/*w*) of blonanserin and different concentrations of IPM. An *in vitro* release experiment was performed and the adhesive performance of the drug-in-adhesive patches with different concentrations of IPM was evaluated by a rolling ball tack test and a shear-adhesion test. The glass transition temperature (T_g) and rheological parameters of the drug-in-adhesive layers were determined to study the effect of IPM on the mechanical properties of the PSA. The results of the *in vitro* release experiment showed that the release rate of blonanserin increased with an increasing concentration of IPM. The rolling ball tack test and shear-adhesion test showed decreasing values with increasing IPM concentration. The results were interpreted on the basis of the IPM-induced plasticization of the PSA, as evidenced by a depression of the glass transition temperature and a decrease in the elastic modulus. In conclusion, IPM acted as a plasticizer on DURO-TAK® 87-2287, and it increased the release of blonanserin and affected the adhesive properties of the PSA.

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1. Introduction

Drug-in-adhesive patch refers to a kind of transdermal system in which the drug and other excipients are dispersed or dissolved in the pressure-sensitive adhesive matrix[1]. The drug must desorb from patches prior to percutaneous absorption, so the drug-release process from the patches is important in the design of a transdermal system[2]. Penetration enhancers are usually added to transdermal patches to enhance drug percutaneous absorption and they were widely investigated for their effects on skin, such as interfering with the lipids or proteins in skin to reduce the barrier resistance of skin[3]. However, the drug-release process from patches can also be altered by the presence of penetration enhancers, and Song et al.[4] proved it by investigating the role of penetration enhancers on bisoprolol tartrate release from patches.

On the other hand, penetration enhancers in transdermal patches may change the physical and mechanical properties of pressure-sensitive adhesive (PSA)[5]. PSA is a kind of adhesive polymer that can stick to a substrate by application of light pressure[6]. The adhesive properties of patches are characterized by adhesion performance tests, such as tack and shear-adhesion. The adhesion performance of patches is strongly dependent on the viscoelastic properties of the adhesive[7]. Several reports have focused on rheological studies to characterize the viscoelastic properties of PSA, and the effect of drug and penetration enhancers on the viscoelastic properties of PSAs has been studied[8–11]. As the viscoelastic nature of PSA controls the adhesion performance and affects the drug-release properties of transdermal patches, changes in the performance of patches can be attributed to a change in viscoelastic nature of PSA.

Isopropyl myristate (IPM) is a commonly used penetration enhancer in topical and transdermal formulations[12]. IPM is known to be safe and has been used in transdermal patches to increase the skin permeation of a large number of drugs, including amlodipine[13], flurbiprofen[14] and azasetron[15]. Its action on skin has been reported, such as integration of drug into the lipid bilayer and promotion of drug solubility in skin[16,17]. Several studies have shown that IPM can affect the adhesive properties of PSA. The incorporation of IPM into a silicon-based PSA increased the flowability and reduced the cohesion strength of the matrix[18]. When IPM was added into an Eudragit E film a decrease in the peel adhesion strength was reported[19]. However, there is lack of study on IPM's role on the drug release process from patches and the mechanism by which IPM influences the adhesive properties of patches is not clear.

Drug release is an important process in the transdermal patch delivery of a drug through the skin, and the adhesive properties of the patch are critical to the safety, efficacy, and quality of transdermal delivery products[20]. In this study, the effect of IPM on blonanserin release and adhesion performance of the drug-in-adhesive patch was investigated. To better understand the influence of IPM on these performances, changes in the mechanical properties of the drug-in-adhesive layers were characterized by glass transition temperature (T_g) and rheological parameters.

2. Materials and methods

2.1. Materials

Pressure-sensitive adhesive DURO-TAK® 87-2287 was obtained from Henkel Corp. (New Jersey, USA). IPM was obtained from China National Medicines Co., Ltd. (Shanghai, China). Blonanserin was purchased from Linyi Shengxin Medicine Science & Technology Co., Ltd. (Linyi, China). All other reagents used were of analytical grade.

2.2. Preparation of adhesive layers and patches

IPM, blonanserin and DURO-TAK® 87-2287 were weighed and dissolved in ethyl acetate and agitated thoroughly with a mechanical stirrer to obtain a homogeneous solution. After evaporation of the ethyl acetate the mixture was used for the DSC test.

Adhesive layers were prepared by coating the above-mentioned solution onto a release liner using a wet film applicator (SLT200, Kaikai Co., Ltd., Shanghai, China). The adhesive layers were dried at room temperature for 10 min and oven-dried for 15 min. After removal of the release liner the adhesive layers with thickness of 500 ± 10 μm were used for rheological tests.

The patches were prepared by first obtaining the adhesive layers. They were then laminated with a polyester baking film (ScotchPak® 9733, 3M, USA). The concentration of blonanserin was 5% (*w*/*w*) based on dry adhesive weight. The concentrations of IPM were set at 0, 4%, 8%, 12% (*w*/*w*) based on the dry adhesive. The thickness of the patches was 80 ± 10 μm and they were used for the experiments of drug release and adhesion performance tests.

2.3. Drug release experiment

Drug release studies were performed ($n = 3$; error bars represent standard deviation) with freshly prepared patches in static Franz cells with a receptor volume of 4.0 mL and a diffusion area of 1.7 cm^2. The receptor compartment contained 0.1% (*v*/*v*) aqueous acetic acid solution to maintain a sink condition at 32 °C and was stirred at 600 rpm with a magnetic stirrer. Circular patches with a diameter of 1.2 cm were attached to circular pieces of Cellophane® membrane with a diameter of 1.6 cm. The membranes with the attached patches were mounted between the donor and the receptor compartment of Franz cells. Two-mL samples were taken at 1, 2, 3, 4, 6, 8, 10 and 12 h and analyzed for drug content. After each sampling the Franz cells were refilled with 2 mL fresh medium.

The determination of blonanserin was performed by HPLC equipped with a Hitachi instrument (Pump L-7100, UV–vis Detector L-7420, T2000L work station) and Diamonsil C18 reversed-phase column (200 mm × 4.6 mm i.d., 5 μm; Dikma Technologies, Beijing, China). The mobile phase was a mixture of methanol and distilled water (with 0.5% triethylamine) at a ratio of 70:30 (*v*/*v*), and the pH was adjusted to 3.5 with phosphoric acid. Aliquots of 20 μL from each sample were injected and eluted at a flow rate of 1.0 mL/min. Measurements were taken at a wavelength of 247 nm and the column temperature was maintained at 40 °C.

2.4. Adhesion performance

2.4.1. Rolling ball tack test

The tack of the adhesive was measured by the rolling ball tack test using a CZY-G primary adhesive tester (Languang M&E Tech Development Center, Jinan, China). A patch with a width of 40 mm and a length of 50 mm was positioned with the adhesive side up on the working surface. A 10.3 mm steel ball was released from the top of the inclined plate (angle 22.5°). The distance was