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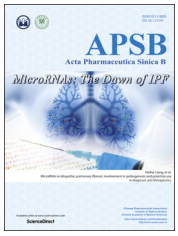

SHORT COMMUNICATION

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

measured from the point where the ball initially was in contact with the adhesive to the position where the ball was stopped. The measurements were performed in triplicate.

2.4.2. *Shear-adhesion test*

The shear-adhesion test was carried out using a CZY-S lasting adhesive tester (Languang M&E Tech Development Center, Jinan, China). The patch was applied to a stainless-steel test panel that was mounted vertically and subjected to a shearing force by a means of a given weight (1000×g) suspended from the patch. The time taken for the patch sample to detach from the test panel was recorded as the value of the shear strength.

2.5. *Differential scanning calorimetry (DSC)*

T_g of the adhesives was measured by Mettler Toledo DSC-1 from −80 to −10 °C at an increasing rate of 5 °C/min. The above-mentioned adhesive solutions were separately packed in an aluminum pan and oven-dried to remove the solvent. The first cycle data were discarded and only the second cycle data were used for determination. The T_g values were determined as the midpoint of the inflection in the DSC thermograms.

2.6. *Rheological tests*

The rheological measurements were performed on an AR 2000ex rheometer (TA Instrument Ltd., USA) equipped with an 8 mm diameter flat-plate. A gap of 500 μm was used. All tests were performed at 32±0.1 °C.

The linear viscoelastic region (LVR) of the sample was determined by strain sweeps from 0.1% to 100% strain at constant frequency (1 Hz). At LVR the material behaves as an elastic solid. Frequency sweeps were conducted after determination of the LVR by strain sweeps.

Frequency sweeps were performed from ω=0.1 to 100 rad/s at a strain of 1% within the LVR. G', G'', and tan δ were determined in dependence of the angular frequency (ω).

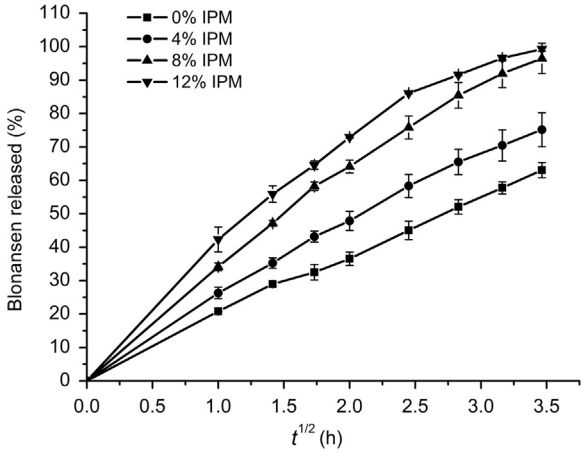

Figure 1 Blonanserin release profile from DuroTak® 87-2287 with different concentrations of isopropyl myristate (IPM) *versus* $t^{1/2}$.

3. Results and discussion

The blonanserin release profiles with different concentrations of IPM were determined, and blonanserin release behavior fitted well with the Higuchi model. The percent of blonanserin released (%) was plotted against $t^{1/2}$ (see Fig. 1). The kinetic constant (k) which is related to drug release rate and the correlation coefficient (r) fitted by Higuchi equation are listed in Table 1. It can be seen that the drug release rate of blonanserin from the patch increased with increasing IPM concentration. The increase of blonanserin release could be attributed to changes in the mechanical properties of the adhesive after the incorporation of IPM.

To further explore the action of IPM in facilitating the drug-release process, changes in the mechanical properties of the drug-in-adhesive layers were investigated by a DSC test and a rheological test.

The data obtained from DSC measurements (Table 1 and Fig. 2) demonstrated that the T_g of DuroTak® 87-2287 containing blonanserin decreased with increasing content of IPM. The T_g is a specific measurement of the chain mobility of polymer[21], so IPM caused an increase in chain mobility of the PSA and acted as a plasticizer. The increase in chain mobility could result in a higher formation frequency of free volume in the PSA[4]. According to the free volume theory, the free volume of the polymer facilitates drug diffusion in a polymer[2]. Therefore, IPM could facilitate blonanserin release by promoting the formation of free volume of the PSA.

PSAs are viscoelastic materials that exhibit both solid- and liquid-like behavior, which is dependent on the frequency of the applied stress at a given temperature[8]. The viscoelastic nature of PSA can be studied by rheological analyses, which does not depend on surface properties of non-physiological substrates used in adhesion performance tests but purely on the material properties[9]. In this study, rheological analyses were determined in terms of "oscillation frequency sweep" to characterize the viscoelastic properties of PSA. The parameters obtained were the complex modulus (G^*) consisting of the elastic modulus (G') and the

Table 1 Release of blonanserin, T_g of the adhesive, rolling ball tack and shear-adhesion test results with different content of isopropyl myristate (IPM) in the patches.

IPM content (%, *w/w*)	Drug release		T_g (°C)	Rolling ball tack test, distance (cm)	Shear-adhesion test, time to failure (h)
	k	r			
0	18.5±0.6	0.997	−54.10	14.9±0.9	12.65±1.26
4	21.6±1.6*	0.996	−60.64	13.5±0.7	3.25±0.39*
8	27.8±1.5*	0.993	−64.16	10.5±1.2*	0.96±0.43*
12	28.2±0.7*	0.978	−65.25	7.7±0.4*	0.52±0.25*

*Statistically significant difference (P<0.05) from the patch without IPM.

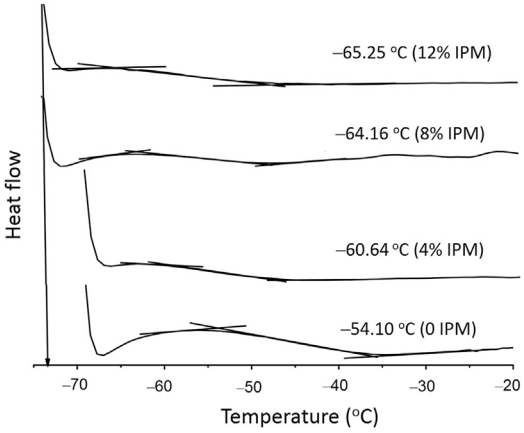

Figure 2 DSC curves of DuroTak® 87-2287 containing 5% (*w*/*w*) blonanserin and different concentrations of isopropyl myristate (IPM).

viscous modulus (G'') (see in Eq. (1)):

$$G^* = G' \cdot \sin(\omega t) + G'' \cdot \cos(\omega t) \quad (1)$$

where the elastic or storage modulus (G') describes the solid-like character and the viscous, or loss modulus (G''), describes the liquid-like character of the PSA[8]. If $G'' > G'$, the material is more liquid than solid. The bonding of PSA occurs at low frequencies and the PSA has to be more liquid-like since it must wet the substrate. The debonding process occurs at high frequencies and requires a solid-like behavior[11]. Therefore, at low frequencies G'' should be predominate and at high frequencies G' should be dominant. The ratio of loss and storage moduli (G''/G') is called loss tangent ($\tan\delta$), which indicates the proportion of dissipated-to-stored energy. Therefore, $\tan\delta$ should be high at lower frequencies as a reduction of G' and should also be high at higher frequencies as an increase in loss modulus[20].

The moduli G', G'' and loss tangent $\tan\delta$ were plotted in dependence of ω at $T = 32$ °C. The moduli G' and G'' increased with rising frequency at all IPM concentrations (Fig. 3). In Fig. 4 the moduli were plotted with increasing IPM concentrations for frequencies of 0.1, 1, 10 and 100 rad/s. It shows that the incorporation of increasing concentrations of IPM into the PSA caused a decrease in the magnitude of G' and G''. In the literature the moduli of a polymer increases with increasing mechanical strength and chain stiffness[22]. The decreased moduli indicated that IPM incorporation caused a decrease in the mechanical strength and resulted in a softer and more relaxed network of the PSA. The reduction in the elastic modulus G' also demonstrated the plasticization effect of IPM on the PSA. The flexibility of the PSA was improved due to the plasticization of IPM by weakening the cohesive interaction between polymer chains. Similar results have been reported on the effect of ibuprofen incorporation into an acrylic pressure-sensitive adhesive[11].

The changes in T_g and rheological moduli with increasing concentrations of IPM could explain the enhancement of the drug-release rate. The lower values of T_g, G' and G'', due to the plasticization effect of IPM represented a less rigid and more relaxed network of the PSA. The incorporation of IPM improved the flexibility of the PSA by increasing the intermolecular separation of the polymer chains and expanded the free volume in the PSA, which facilitated the release of blonanserin from the patches. Hence the more IPM was included in the formulation the

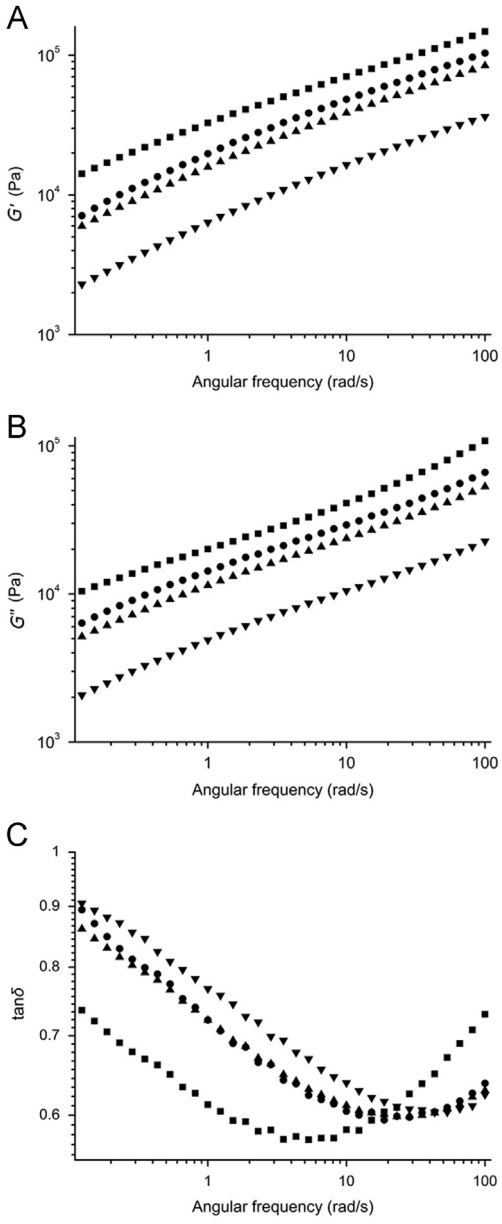

Figure 3 Oscillation frequency sweep data of DuroTak® 87-2287 containing 5% (*w*/*w*) blonanserin with no IPM (■) and with 4.0% (●), 8.0% (▲), 12.0% (▼) IPM, respectively. The elastic modulus G' (A), the viscous modulus G'' (B), and the damping factor $\tan\delta$ (C) are plotted *versus* the angular frequency (ω).

faster drug release could be achieved. Wang et al.[23] also reported similar results of the effect of liquid paraffin on drug release from patches based on a styrene–isoprene–styrene thermoplastic elastomer copolymer.

PSA is a critical substance present in transdermal patches that is responsible for physico-mechanical properties of the patch, drug release, etc.[9]. Changes in the thermodynamic and rheological properties of PSA after the addition of IPM can affect the adhesion performance of the patches.

In the rolling ball tack test, the distance traveled by the ball on the patch was measured as tack. Tack is the ability of an adhesive to adhere quickly to another surface and a shorter stopping distance means higher tack[20]. The data obtained is listed in

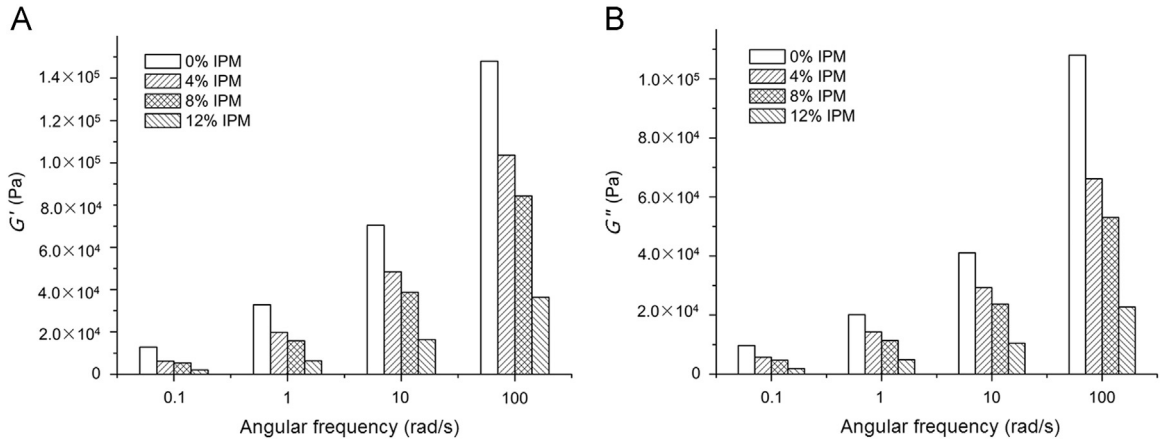

Figure 4 Elastic modulus G' (A) and viscous modulus G'' (B) of DuroTak® 87-2287 containing 5% blonanserin (*w*/*w*) with increasing concentrations of isopropyl myristate (IPM) at the angular frequency of 0.1, 1, 10 and 100 rad/s.

Table 1 and it was shown that the distance traveled by the ball decreased with increasing IPM concentration in the formulations. This indicated that the tack of the patch increased with increasing IPM concentration. Taking the results from DSC and rheological tests into consideration, the effect of IPM on the tack of the patch can be well explained. In the bonding process the lower moduli value indicated increased flexibility of the PSA, that is, the incorporation of IPM made the PSA deform easily when in contact with the substrate, allowing it to adhere more easily to another substrate.

After application of a transdermal patch the PSA should remain attached to the skin for a specific period of time despite tangential stresses caused by both body movements and cloth friction[20]. Shear-adhesion characterizes the resistance of a PSA to tangential stresses, that is, the cohesion of the adhesive[11]. The shear-adhesion test determined the time necessary to remove a standard area of the patch from the plate under a standard load. In the test, the adhesive failed cohesively, leaving some adhesive residue on the adherent plate and some on the backing layer. The results are shown in Table 1 and it was shown that the shear-adhesion decreased significantly with increasing concentrations of IPM. The time to failure decreased from 12.66 to 0.53 h with increasing IPM concentration from 0 to 12%. This result indicates that the cohesive strength of the PSA was reduced by IPM incorporation. The changes in the shear-adhesion of the patches coincided with the effect of IPM on the mechanical properties of the PSA. On addition of IPM, the PSA became softer and the entanglement in the polymer was reduced. Hence the cohesive interactions between the polymeric chains were weakened by the presence of IPM.

Taking these results together, the plasticization effect of IPM on the PSA caused the enhancement of drug release, an increase in the tack and a decrease in the shear-adhesion. Usually, most formulation studies have focused on the maximum flux of drug through the skin. The findings above indicate that additives in transdermal patches could change the adhesive properties of the patch. If more transdermal systems are to be developed further study of specific adhesive–drug-permeation enhancer systems is essential.

4. Conclusions

In conclusion, the incorporation of IPM into the drug-in-adhesive transdermal patch in which 5% blonanserin was dissolved in DURO-TAK® 87-2287 caused an enhancement of drug release, an increase in the tack and a decrease in the shear-adhesion. This phenomenon is attributed to the plasticization effect of IPM on the PSA. The results indicated that the drug release and adhesion performance of a transdermal patch are related to the mechanical properties of the adhesive, which in turn would be affected by addition of permeation enhancers. In addition, the effect of permeation enhancers on drug release and mechanical properties of the PSA should be taken into consideration in transdermal patch formulation studies to ensure the proper viscoelastic properties of the transdermal patch. There may be a trade-off between drug release enhancement and adhesive properties of the transdermal patch after the addition of permeation enhancers.

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